



# **SURGERY OF THE ADRENAL GLANDS**

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AMERICAN LECTURE SERIES®

*A Monograph in*

AMERICAN LECTURES IN ABDOMINAL VISCERA

*Edited by*

LESTER R. DRAGSTEDT, M.D.

*Chairman, Department of Surgery  
University of Chicago, The School of Medicine  
Chicago, Illinois*

# SURGERY OF THE ADRENAL GLANDS

*By*

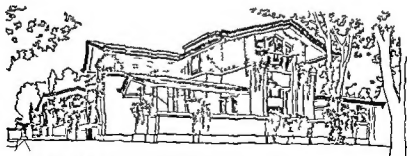
**WILLIAM WALLACE SCOTT M D PH D**

*Professor of Urology The Johns Hopkins University School of Medicine  
Urologist in Charge The Johns Hopkins Hospital  
Director James Buchanan Brady Urological Institute  
Baltimore Maryland*

*and*

**PERRY B HUDSON M D**

*Assistant Professor of Urology  
Columbia University College of Physicians and Surgeons  
Assistant Urologist Presbyterian Hospital  
Assistant Visiting Urologist Francis Delafield Hospital  
New York New York*



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**SURGERY OF THE  
ADRENAL GLANDS**



# I

## INTRODUCTION

**DURING THE** last 30 years remarkable advances have been made in our knowledge of the normal and abnormal adrenal gland. These have included among many recognition and successful surgical treatment of functioning tumors of both the adrenal cortex and medulla isolation and synthesis of a number of crystalline adrenal hormones utilization of these steroids in the treatment of adrenal insufficiency secondary to disease or removal of the adrenals extensive exploration of the biologic properties of these compounds in health and disease and inquiry into the effects of partial and complete adrenalectomy in several disease states. Whereas it is beyond the scope of this monograph to review adequately the mass of clinical and laboratory data which pertain to these advances it is necessary to present in an abbreviated fashion certain current concepts of adrenal function which relate to the diagnosis and treatment of adrenal states amenable to surgical therapy.

In presenting the clinical picture of patients with adrenal tumors representative examples have been chosen and their clinical histories given in detail. This is done in the belief that this method of presentation provides a clearer picture of each condition than that which is furnished by a listing of the frequency of symptoms in a large



## II

### DEVELOPMENT

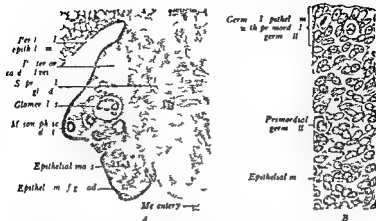
ACCORDING TO WITSCHI<sup>119</sup> in birds and reptiles where the origin of the adrenal is most easily studied the adrenal cortex arises from dorsally situated strings of cells derived from the blastema cords along the median borders of the mesonephric bodies. Ventrally situated cells from the same area take part in the formation of the primordial gonad folds contributing the medulla of the gonad. Thus the adrenal cortex and gonad medulla have a common origin in the mesonephric blastema and are of mesodermal origin. This common origin of adrenal cortex and gonad medulla the latter giving rise to the interstitial cells of the testis or the theca cells of the ovary has caused several authors to suggest that at times cells potentially capable of forming gonadal hormones may be included in the adrenal.

In man the first traces of the adrenal cortex are found at the beginning of the fourth week of life (6 mm embryo) at which time cells which lie between the mesonephric fold and the root of the mesentery begin to proliferate<sup>110-134</sup>. At this time and for a short time thereafter coelomic epithelium is in direct continuity with subjacent mesenchyme (Figure 1 A and B). Rapid growth occurs and at 12 mm prominent mesenchymal condensations are evident (Figure 1 C Figure 2 A and B). With fur



series of cases. It will become evident that many of the examples presented have been studied by our colleagues particularly Dr. Lawson Wilkins and Dr. John Eager Howard. We are indebted to them not only for permission to use case material but also for their unfailing cooperation in the clinical management of these and other patients with adrenal disorders. We are convinced that this cooperation between internist and surgeon cannot be emphasized too strongly. We are also deeply indebted to the many scholars in medicine who have done so much to increase the accuracy of diagnosis of adrenal disorders and to improve treatment. We have given credit where credit seemed due.

We hope that the reader will profit directly from this presentation and more important that he will be stimulated to read authoritative source material presently available and appearing in increasing volume.



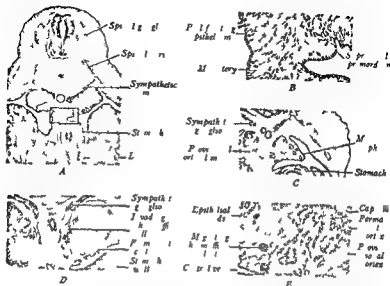


Figure 1 Development of the human suprarenal gland shown in transverse sections A at 8 mm ( $\times 24$ ) B detail of area marked by a rectangle in A ( $\times 75$ ) C at 12 mm ( $\times 20$ ) D at 16 mm ( $\times 24$ ) E at four months ( $\times 70$ )

ther increase in size the enlarging adrenal cortex projects from the dorsal wall of the coelom between the urogenital organs and the mesentery. Here they continue to enlarge becoming relatively huge. In an eight weeks embryo the adrenal is as large as the kidney and at birth is one third as large.

The adrenal medulla is of ectodermal origin arising in common with sympathetic ganglion cells from primitive cell masses of the neural crest. In human embryos of 16 mm when the provisional cortical mass is surrounded by permanent cortex masses of cells derived from the primitive sympathetic ganglia grow ventrally and penetrate the cortical primordium on its medial side (Figure 1 A B C D and E). At this stage they begin to exhibit the chromaffin reaction. Continued migration of the e cells

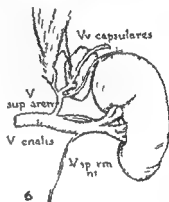
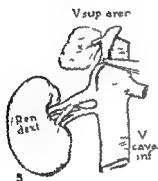
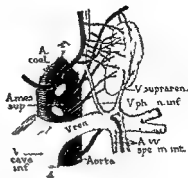
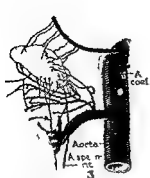


Figure 3 Renal and suprarenal arteries right side

Figure 4 Renal suprarenal and associated arteries and veins left side

Figure 5 Renal and suprarenal veins right side Suprarenal vein as regularly is short renal vein paired represents a relatively uncommon arrangement

Figure 6 Renal suprarenal and tributary veins left side Renal vein of standard type receives suprarenal phrenic and capsular drainage cranially caudally it receives gonadal (here spermatic) vein

cortex can be divided histologically from without inward into three vaguely defined layers the zona glomerulosa, zona fasciculata and zona reticularis (Figure 7) Based on the distribution of doubly refracting lipid drop

### III

## STRUCTURE

IN THE ADULT the adrenal glands are paired yellowish in color, flattened and triangular to semilunar in shape measure approximately  $4.0 \times 2.5 \times 0.5$  centimeters weigh 3.5 to 5.0 grams each and are situated at the cranial end of each kidney. Atrophy can be recognized grossly the gland appearing paler thinner and smaller than the normal but hyperplasia may be difficult to recognize either grossly or microscopically.

The blood supply is considerable and variable. Anson *et al*<sup>6</sup> have shown that the adrenal arteries derived from the inferior phrenic aortic and renal arteries may be exceedingly numerous at times their number attaining a total of 50 or more at the periphery of the gland (Figures 3 and 4). No similarity in pattern exists between arteries and veins. Whereas adrenal arteries are numerous and small adrenal veins are single large and constant in pattern. On the right side the adrenal vein is short and empties directly into the venacava (Figure 5). On the left side the vein is longer commonly joins the inferior phrenic and empties into the renal vein opposite the termination of the internal spermatic (Figure 6). Grollman<sup>30</sup> and others<sup>39-43</sup> have described the circulation within the gland itself. Owing to differences in arrangement and shapes of the constituent cells the adrenal

tivity. However according to Sayers<sup>119</sup> The battery of specialized staining technics which have been applied to the adrenal has contributed little more to our knowledge of the chemistry and physiology of the adrenal cortex than has the simple Sudan method. It is recognized that the amount of lipid present as measured by intensity of Sudan stain may not parallel material exhibiting steroid reactions (birefringence fluorescence Schiff reaction<sup>1147</sup>). However until more is known about the chemical nature of the latter materials it is wise to withhold physiological interpretations. Statements regarding storage and secretion of ketosteroids have contributed nothing but confusion to the field. Furthermore he considers it premature to assign distinct secretory functions to the zones when the problem of the nature of the secretion of the adrenal cortex is not yet settled."

Newer technics should aid in this regard particularly if applied to fresh adrenal tissue rather than that oxidized by fixation. Some believe that the mitochondria are involved in hormone production.

The border between the cortex and medulla is made irregular by projections of columns of cortical cells into the medulla. The irregularly shaped cells of the medulla are arranged in closely packed groups surrounded by sinusoidal venules. As early as 1856 Vulpian<sup>139</sup> noted a striking difference in the staining reaction of the cells of the cortex and medulla the latter turning green when immersed in a solution of ferric chloride. Shortly thereafter Henle<sup>5</sup> noted that when adrenal tissue was allowed to react with dilute solutions of potassium dichromate certain granules in the medullary cells appeared brownish red with precipitate. This is the so called "chromaffin reaction" and is explained on the basis of reduction of dichromate to insoluble chromium dioxide by epinephrine or a precursor. It appears to some that the chro

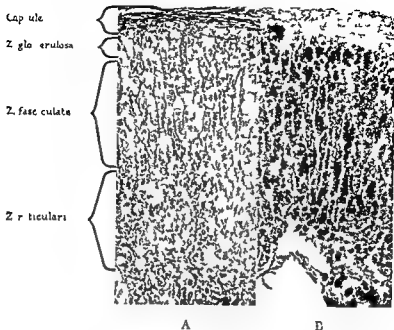


FIGURE 7. Sections of the adrenal gland of a normal adult male. A. hematoxylin and eosin ( $\times 75$ ). B. oil red O and eosin ( $\times 75$ ).

lets in certain cells of the cortex. Weaver and Nelson<sup>14</sup> have defined four zones. The epithelial cells comprising these layers vary from groups of small columnar cells in the glomerulosa to larger polyhedral cells arranged in columns in the fasciculata to large dark and small light cells in the reticularis. According to Hoerr,<sup>15</sup> these dark and light cells are especially evident in the guinea pig. There seems to be fair unanimity of opinion that the cells of the cortex originate in the zona glomerulosa and as they develop migrate inward to degenerate in the most inward layer, the zona reticularis.

Numerous histologic techniques have been devised in an effort to identify and localize the steroids of the adrenal cortex and to measure their functional and secretory ac-

## IV

### FUNCTION

#### THE ADRENAL CORTEX

FOR A DETAILED discussion of the physiology of the adrenal cortex the reader is referred to the extensive writings of Albright<sup>3</sup> Ingle<sup>4</sup> Kendall<sup>14</sup> Long<sup>15</sup> Sayers<sup>119</sup> Selve<sup>1</sup> and others. However a few observations relating to adrenal cortical function will be outlined including those functions which seem to be altered in the chronic hyperfunctioning state commonly observed in the patient with adrenal hyperplasia or tumor. Admittedly in cases of hyperplasia or tumor we may be dealing with an aberrant secretory activity which has no necessary relation to the normal physiology of the adrenal cortex.

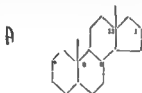
All workers agree that the adrenal cortex unlike the medulla is essential for life and that such essentiality depends on the elaboration of a hormonal substance or substances by the gland. To date although 28 crystalline steroids have been isolated from adrenal tissue it is not clear which steroid or combination of steroids is normally elaborated by the cortex or which is necessary for life. Some investigators believe that one parent hormone is elaborated and in turn its metabolites exert observed functions of known crystalline steroids; others believe that several different steroids are made and individually secreted into the blood stream. Of importance is the observation



maffin reaction is roughly proportional to the epinephrine content of the gland. Of interest to the subsequent discussion of medullary tumors of the adrenal is Karsner's<sup>73</sup> view that a diagnosis of a pheochromocytoma is not valid without a positive chromaffin reaction.

a carbonyl or an hydroxyl group. There are four known examples of this the most studied being 11 dehydro 17 hydroxycorticosterone known also as cortisone or compound E of Kendall (Figure 8B)

Steroids having androgen, estrogen and progestational actions have been isolated from the adrenal gland. Examples are androsterone, estrone and progesterone. Normally estrogen and progestational actions appear to be relatively weak and quantitatively these steroids make up only a small percentage of the total steroidal material of the adrenal. However it will be seen that in certain pathologic states notably hyperplasia and tumor feminizing changes occur and urinary estrogens may be increased. Adrenal androgens appear to be concerned with the growth of axillary and pubic hair and with muscular vigor.



Common basic ring system

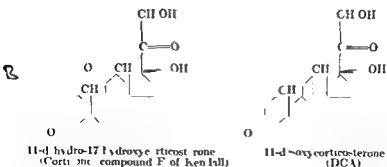


Figure 8 Basic steroid ring system illustrating the component rings and the conventional number assigned to the individual carbon atoms. Below are two crystalline adrenal cortical steroids.

that the amorphous fraction which remains after all crystalline steroids have been separated from cortical extracts is still capable of sustaining life in the adrenal ectomized animal. With the increasing availability of crystalline adrenal steroids it may well be that important discoveries will be made concerning which hormone is most effective in maintaining life. The recent work of Thorn *et al*<sup>13</sup> and Huggins and Bergenstal<sup>14</sup> attests to this. Both groups have succeeded in maintaining life in humans after bilateral adrenalectomy with compound E (cortisone) a feat which was extremely difficult when only cortical extracts and desoxycorticosterone acetate were available (Huggins and Scott)<sup>15</sup>

Present knowledge indicates that the adrenal cortex is concerned in part with a number of metabolic activities which include 1) the metabolism of sodium potassium chloride and water 2) certain aspects of the metabolism of carbohydrate protein and fat and 3) activities similar to those produced by certain gonadal hormones. Activities described under headings 1) and 2) have been labeled corticoid and those under heading 3) as androgenic, estrogenic and progestational.

All crystalline adrenal cortical steroids have a common basic structure as shown in Figure 8A which in turn is common to certain gonadal hormones, cholesterol and vitamin D. Differences in action appear to depend in part upon modification of this nucleus primarily in position 3, 11 and 17. Thus the chief example of a steroid having a pronounced effect on mineral metabolism is 11 desoxycorticosterone (Figure 8C). This compound has little effect on carbohydrate metabolism and structurally is seen to lack an oxygen atom at position 11.

Steroids which in part are concerned with metabolism of protein and gluconeogenesis have in common an oxygen atom at position 11, this oxygen being in the form of

malize plasma sodium regardless of the direction of the deviation from normal whereas DCA acts unidirectionally to produce sodium retention

More will be said concerning possible androgen production by the adrenal later on when the rationale for bilateral adrenalectomy in the treatment of disseminated prostatic cancer is discussed. At this point a brief discussion of urinary 17 ketosteroids and corticoids seems warranted to aid in a discussion of the physiology of the normal adrenal cortex and in the diagnosis of the clinical conditions of adrenal cortical hyperplasia and tumor.

### Urinary 17 ketosteroids

Urinary steroids of the general configuration of those already shown in Figure 8 but having a ketone group in position 17 are known as 17 ketosteroids. Such steroids when allowed to react with *meta* dinitrobenzene in alkaline solution (Zimmermann reaction) give rise to a magenta color which can be measured quantitatively. The method of extraction, separation and determination which we now rely upon is essentially as follows:

The urine is collected in glass bottles containing 10 ml of concentrated hydrochloric acid as a preservative. Subsequently a 100 ml aliquot is hydrolyzed by boiling for 20 minutes after addition of 0.1 of its volume of concentrated hydrochloric acid. It is then cooled quickly and extracted by shaking with ether in a centrifuge bottle. Shaking is accomplished by a mechanical shaker and separation by centrifugation and aspiration of the supernatant ether layer. This ether layer is then washed several times with base in order to remove acids and phenols. This extract after acidification, washing with water, evaporating to dryness and solution in absolute alcohol is termed the "neutral extract" and is ready for colorimetric determination of the total neutral 17 ketosteroids. To 0.2 ml of test

Furthermore they are believed to be responsible for the total amount of urinary 17 ketosteroids found in the urine of women and roughly two-thirds of that found in the urine of men (*vide infra*)

At this point it appears appropriate to pause and to introduce a direct quotation from a recent review article by Ingle<sup>71</sup> entitled *The Biological Properties of Cortisone*. This should serve to emphasize that rigid assignment of function to crystalline adrenal cortical steroids should be avoided whether these steroids are elaborated by the normal cortex or the cortex involved in hyperplasia or tumor. Ingle states: "If any one fact has been made evident about cortisone it is that this substance affects many different tissues and physiologic processes of the body. At a time when the physiology of the adrenal cortex seemed more simple cortisone and related 11 oxygenated steroids were tagged as S or sugar hormones or glucocorticoids. The author is not without sin in this matter of describing an elephant in terms of shape of its tail and was among the students of endocrinology who found these characterizations useful but he believes that this is an appropriate time to abandon the concept that cortisone is concerned principally with carbohydrate metabolism and to explore each of its many biologic properties in search for new concepts of its action. As an antidote for an era of oversimplification in adrenal physiology the author recommends the masterful review of the adrenal cortex and homeostasis by Sayers."<sup>119</sup>

In this review Sayers<sup>119</sup> cites many investigations in support of new concepts of cortisone action. Thus Loisham *et al*<sup>41</sup> have shown that cortisone will maintain serum electrolytes within the normal range in most patients whose adrenals have been removed whereas desoxycorticosterone (DCA) usually will not. This fits in with the concept of Woodbury *et al*<sup>1</sup> that cortisone can nor

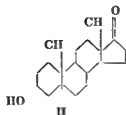
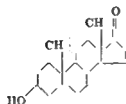
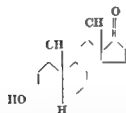
Androsterone  
(alpha)Dehydroandrosterone  
(beta)Etiocholanolone  
(alpha)

Figure ■ Structural formulae of three normally occurring neutral urinary 17 ketosteroids. They are characterized as *alpha* or *beta* 17 ketosteroids depending on the *alpha* (---) or *beta* (—) orientation of the OH group at the third carbon.

Normal men excrete on an average more 17 ketosteroids than do normal women. Whereas daily variations are appreciable, our average values are 14 mg per 24 hours for men and 9 mg for women. This difference in average of 5 mg is believed to represent the amount derived from the testes; the 9 mg is thought to originate in the adrenal cortex of both sexes. Evidence indicates that the amount contributed by the ovaries is very small. Women with severe adrenal insufficiency excrete very little of these compounds. Thus it would appear that the

solution in an Evelyn colorimeter tube is added 0.2 ml of a 2 per cent solution of *meta* dinitrobenzene and 0.2 ml of 2.5 N potassium hydroxide both in absolute alcohol. The color is developed in the dark at 25°C for 80 minutes and after dilution with 10 ml of absolute alcohol the intensity of color is determined in the Evelyn colorimeter using a 520  $m\mu$  filter. Absolute alcohol is substituted for the neutral extract in the blank. Dehydroisoandrosterone is used to prepare standards and as a reference.

Little difficulty has been encountered with the method except in preserving the alcoholic potassium hydroxide solution. However we have found as have Wilson and Carter<sup>148</sup> that this solution will keep well if ascorbic acid is added and if stored under nitrogen.

Whereas a number of these steroids exist in the urine of normal individuals three predominate: androsterone, its isomer etiocholanolone and dehydroisoandrosterone (Figure 9). Androsterone and etiocholanolone appear in about equal quantities and in greater concentration than dehydroisoandrosterone. Androsterone is a stronger androgen on bioassay than dehydroisoandrosterone (approximately three times). Etiocholanolone is inactive. Because of this and other examples which could be given it is important to emphasize that *all urinary 17 ketosteroids are not androgens*.

Due to spatial variations of the hydroxyl group in position 3, 17 ketosteroids are divisible into *alpha* and *beta* fractions. *Beta* 17 ketosteroids are precipitated with digitonin and can be measured colorimetrically.<sup>5, 31, 4</sup> Androsterone and etiocholanolone are *alpha* 17 ketosteroids; dehydroisoandrosterone is a *beta* 17 ketosteroid. Whereas normally 0 to 15 per cent of the total level of 17 ketosteroids consists of the *beta* fraction, in certain altered states to be described this fraction constitutes a much greater percentage of the total.

Those having similar biological properties on bioassay have been named biocorticoids those having similar chemical properties by chemical assay have been designated chemocorticoids

**Urinary Biocorticoids** Suitable extracts of human urine when injected into the adrenalectomized animal will effect several actions characteristic of certain adrenal cortical extracts and crystalline steroids. Thus they may maintain life<sup>13</sup> prevent water intoxication<sup>14</sup> promote deposition of glycogen in the liver<sup>33</sup> prolong survival from exposure to cold<sup>34</sup> and improve work performance<sup>14</sup>. Quantitative bioassays based on cold protection and liver glycogen deposition have been developed and are referred to as the CP test and the LGD test respectively. Whereas the LGD test is less sensitive than the CP test it is more accurate<sup>34, 35</sup>. Apparently both measure essentially the same thing for corticosteroids possessing an oxygen atom at position 11 will promote glycogen deposition and prolong survival from exposure to cold.

Although there is a close correlation between the rate of urinary excretion of these biocorticoids and the activity of the adrenal cortex as judged clinically these procedures require precise technique and are time consuming. Consequently they are not practical in most clinical laboratories.

**Urinary Chemocorticoids** The chemical techniques used to estimate urinary chemocorticoids are based on the ability of a number of steroids to reduce copper or phosphomolybdic acid<sup>36</sup> or to generate formaldehyde by reaction with periodic acid<sup>37, 38</sup>. Based on these properties urinary lipids have been given the designation CRL if they reduce copper PRL if they reduce phosphomolybdic acid and FL if they generate formaldehyde.

For example steroids containing a primary or secondary *alpha* ketol group an *alpha* beta unsaturated 3



testes and the adrenals are the principal sources of the urinary 17 ketosteroids. Direct evidence for this (admittedly complicated by severe malignant disease) is found in the single adult male studied by Huggins and Scott<sup>63</sup>. This individual survived bilateral adrenalectomy after previous castration for approximately four months without cortisone therapy and total urinary 17 ketosteroids fell to extremely low levels.

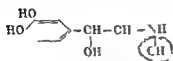
Whereas it seems reasonably clear that the testes and the adrenal cortex are responsible for these steroids, their precursors in these organs are poorly understood. Some clinicians have considered the urinary 17 ketosteroids to be an index of androgenic activity of these structures but it must be again emphasized that all urinary 17 ketosteroids are not biological androgens.<sup>6</sup> Furthermore, recent evidence suggests that cortisone itself is degraded by the liver and other tissues to 17 ketosteroids and perhaps even androgens. Thus the administration of ACTH or cortisone leads to a rise in these urinary elements.

Whereas it will be clear that the determination of total urinary 17 ketosteroids and the *beta* fraction are of considerable importance as laboratory aids in the diagnosis of certain disorders of the testes and adrenals, it would appear at present that their output is not a sensitive measure of changing rates of secretion of cortical hormone by the adrenal cortex in man, particularly over short periods of time. Recent evidence suggests that the measurement of urinary corticoids may prove superior and that as a consequence a brief discussion of these substances seems justified.

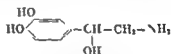
### Urinary Corticoids

The term urinary corticoid has been used to describe substances in urine which are not clearly identified but which possess certain properties of the cortical hormones.

Extracts of the adrenal medulla capable of causing a pronounced rise in blood pressure upon injection were first prepared by Oliver and Schrfer <sup>101</sup> in 1895. In 1901 Takamine <sup>131</sup> and Aldrich <sup>4</sup> independently succeeded in isolating crystalline 1 adrenaline to which Aldrich assigned the correct empirical formula  $C_9H_{13}O_3N$ . Due to the efforts of many including the synthesis of racemic adrenaline by Stoltz <sup>13</sup> and Dakin <sup>8</sup> in 1905 the structural formula shown below was established.



EPINEPHRINE  
(Adrenaline)



NOREPINEPHRINE  
(Arterenol)

The term "epinephrine" proposed by Abel <sup>1</sup> remains official for the natural substance. 1902

Whereas it is beyond the scope of this monograph to discuss at length the various metabolic changes secondary to the administration of epinephrine — such as increases in blood sugar, blood lactic acid and basal metabolic rate — a brief description of its "sympathomimetic" action should aid in the subsequent discussion of the diagnosis and treatment of functioning adrenal medullary tumors.

An understanding of sympathomimetic action presupposes a familiarity with current concepts of neurohumoral transmission in the autonomic nervous system. On *anatomic* grounds the autonomic nervous system may be divided into parasympathetic (craniosacral) and sympathetic (thoracolumbar) divisions. On *functional* grounds division is made on the basis of the nature of the substance liberated in the region of the postganglionic nerve ending of all autonomic nerve fibers, whether excitatory or inhibitory. At present many believe that acetylcholine

ketone group or both will reduce phosphomolybdic acid. In this category are to be found a number of biologically active steroids including cortisone, desoxycortisone and progesterone as well as a large number of biologically inactive steroids. Copper is reduced by steroids containing an *alpha* ketol group but an *alpha* *beta* unsaturated 3 ketone group does not react.<sup>4</sup> Formaldehyde is liberated from 20, 21 *alpha* ketols and glycols by oxidation with periodic acid.<sup>35, 36</sup>

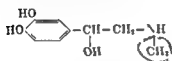
Until recently the above methods have been applied to chloroform or chloroform ether extracts of urine and measure the chemocorticoid present in the free state. Since 1951 several laboratories<sup>6, 113, 136</sup> have investigated procedures designed to measure conjugated (and total) urinary corticosteroids in addition to the free moiety. Those interested should read the article by Reddy, Jenkins and Thorn.<sup>113</sup> They believe that their method measures only total 17 hydroxycorticoids. If so many nonspecific substances will be eliminated and a better correlation should be possible between chemocorticoid excretion and the clinical estimate of adrenal cortical activity as well as with the level of urinary biocorticoids.

One distinct advantage of the chemical methods over those involving bioassay is their simplicity making them suitable for routine determination in the clinical laboratory. The next few years should see a greater application of these studies in known states of adrenal function and should permit a more accurate evaluation of their worth.

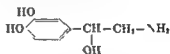
## THE ADRENAL MEDULLA

Most of our knowledge of medullary function is based on laboratory and clinical observations following the injection of epinephrine or on the measurement of epinephrine and epinephrine like substances in the blood during various physiologic manipulations.

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is liberated at all postganglionic parasympathetic nerve endings resulting in transmission between the nerve fiber and receptor in the cell ( myoneural junction ) Such fibers have been termed cholinergic

Whereas the majority of postganglionic sympathetic nerve fibers liberate an adrenaline like substance and are known as adrenergic types some sympathetic fibers — such as those innervating vasodilator fibers and the sweat glands in some species — are cholinergic (Figure 10) Sympathomimetic implies mimicry of only those actions of the adrenergic type whether excitatory or inhibitory but not cholinergic sympathetic action Some of the more important sympathomimetic actions of epinephrine are cardiac acceleration arteriolar constriction pupillary dilation salivary secretion relaxation of bronchial musculature and inhibition of the urinary detrusor

According to the late W B Cannon and his school excitatory or inhibitory actions of the adrenergic type depend upon the combination of epinephrine with either

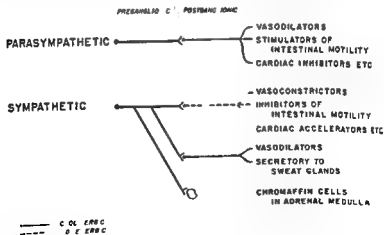
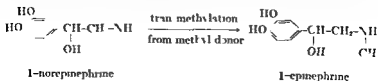


Figure 10 Schematic representation of the autonomic nerve fibers indicating the sites of action presumed nature of the chemical mediator and types of response

an excitatory substance E or an inhibitory substance I at the receptor with the formation of sympathin E and "sympathin I" respectively. Recently a number of reports have appeared which tend to clarify this mechanism.

After Abels<sup>1</sup> characterization of epinephrine most conceded that it represented the pressor component of the adrenal medulla and some believed epinephrine and sympathin I were identical although the pharmacologic action of epinephrine was not strictly that observed following sympathetic nerve stimulation. Subsequent to this Burger and Dale<sup>10</sup> synthesized a large number of *beta* phenylethylamine analogs which on test showed a general similarity of action to that observed following sympathetic nerve stimulation and to which they gave the designation sympathomimetic amines. Among these were epinephrine and norepinephrine the latter differing in structure from epinephrine by absence of a methyl group attached to nitrogen at the end of the side chain (Nitrogen Ohne Radical) as shown above. Although Burger and Dale pointed out biologic differences in these two compounds it remained for Bacq<sup>9</sup> to suggest that the action of norepinephrine simulated the properties of sympathin E.

It now appears to most workers that on stimulation some sympathetic nerve fibers release only epinephrine others liberate only norepinephrine and still other adrenergic nerve endings yield both. Furthermore it seems likely that most adrenergic nerves are capable of trans methylating norepinephrine thus forming epinephrine.



These observations and speculations are particularly interesting in view of the finding of Goldenberg *et al*<sup>44</sup> and others<sup>32 54</sup> that epinephrine extracts from normal adrenal glands as well as from pheochromocytomas may contain relatively large amounts of norepinephrine at times as much as 50 to 90 per cent. This may result from an impairment of norepinephrine transmethylation.

In passing it is of interest to note that pharmacologically dibenamine, one of the drugs used to test patients for the presence of a pheochromocytoma, acts only against norepinephrine, not epinephrine. Hence it would be reasonable to assume that if a pheochromocytoma were producing mainly epinephrine, such a competitor as dibenamine might give a false negative test.

## V

### TUMORS OF THE ADRENAL GLAND

VARIOUS CLASSIFICATIONS have been proposed for tumors arising within the adrenal cortex and medulla. Generally such have been based on either the microscopic appearance of the tumor or the signs and symptoms observed in patients with proved tumors.

#### ANATOMIC CLASSIFICATION

The anatomic classifications of Karsner<sup>73</sup> and Stout<sup>10</sup> appear to be the most recent and complete and the reader is referred to their original manuscripts for details. In brief, all tumors are separated into two broad divisions: 1) heterologous and 2) homologous, and the latter subdivided into cortical and medullary.

#### Heterologous Tumors

Heterologous tumors are those derived from tissues within the gland which are not peculiar to the adrenal and which may occur in any other gland. These include fibroma, lipoma, neuroma, neurofibroma, myoma, hemangioma, lymphangioma, myelolipoma, and melanoma. Karsner believes that osteomas probably represent metaplasia following inflammation or hemorrhage and that the spindle and giant cell sarcomas reported in the earlier literature probably were anaplastic carcinomas and syphilicogonionomas respectively.



**Homologous Tumors**

**Cortical Tumors** The principal tumors arising from the adrenal cortex are the cortical nodule the cortical adenoma and the cortical carcinoma. The so called cortical nodule or hamartoma resembles closely the cortical adenoma but is usually smaller multiple bilateral and somewhat more regular in cellular arrangement. Both are benign and are usually encapsulated. The origin of the adenoma is obscure some believing that it arises from primitive cortical cells and others from mature cortical cells. It may possibly arise from a cortical nodule.

Cortical carcinomas are distinguished from cortical adenomas primarily on histological evidence of invasion and clinical evidence of metastasis.

Examples of the histology of cortical adenomas and carcinomas as well as certain medullary tumors will be presented below under representative clinical cases.

**Medullary Tumors** Under this heading most authors group all tumors which seem to arise from the sympathogonia a primitive cell common to sympathetic ganglia and the adrenal medulla or to one of its descendants. According to Bielschowsky " the sympathogonia may differentiate along two lines forming the sympathoblast and the pheochromoblast. Each in turn may give rise to the sympathetic ganglion cell and pheochromocyte respectively the latter being known as a chromaffin cell and positively identified only by the chromaffin reaction. Tumors arise from all these cells and the preponderant cell type forms the stem for the descriptive term used thus sympathicogonioma sympathicoblastoma ganglioneuroma and pheochromocytoma.

Some authors group sympathicogoniomas and sympathicoblastomas together under the heading neuroblastoma and Stout classes neuroblastomas and differentiated

and undifferentiated sympathicogoniomas under sympathicoblastoma

Ganglioneuromas have been described as differentiated ganglioneuroma (benign) and partially differentiated ganglioneuroma (malignant) by Stout and ganglioneuroma (generally benign) and malignant ganglioneuroma by Karsner

The term paraganglioma is used by many synonymously with pheochromocytoma. Stout prefers to call hormonally active tumors of the paraganglionic group pheochromocytomas and all inactive ones paragangliomas in each instance naming the region or tissue of origin an example of the latter being a paraganglioma of the carotid body

If a pheochromocytoma shows histologic invasiveness or clinical metastasis some use the term pheochromoblastoma

## FUNCTIONAL CLASSIFICATION

Several authors including Cahill *et al*<sup>10</sup> Kenyon<sup>7</sup> and Wilkins<sup>146</sup> have divided adrenal cortical tumors into two main groups according to whether or not they are hormonally active (with subdivision of the latter group according to the symptom complexes observed). Medullary tumors can also be divided into two main groups on the basis of their hormonal activity but subdivision of the functional group is not yet possible. For pedagogic reasons such a classification offers certain advantages but it should not be too rigid. As Kepler and Locke<sup>18</sup> have so aptly expressed it such a classification may "have the disadvantage of developing unconscious psychologic barriers which confine thinking to artificially imposed limitations." With reservations and without originality the following classification is presented.

**Cortical Tumors**

- 1 Tumors with no recognizable hormonal activity
- 2 Tumors having hormonal activity leading to
  - A Cushing's syndrome with or without virilization
  - B Virilization
    - i In the male child
    - ii In the female child
    - iii In the adult female
  - C Feminization
    - i In the male child
    - ii In the adult male

**Medullary Tumors**

- 1 Tumors with no recognizable hormonal activity
- 2 Tumors having hormonal activity

**Hormonally Inactive Cortical Tumors**

We have had little personal experience with tumors in this group and have not reviewed the literature in this regard. According to Cahill,<sup>6</sup> Hartung, Macera, Stevenson, Gibson and others have reported tumors of the adrenal cortex which have occurred without recognizable hormonal changes. In his most recent review with Melnicow,<sup>7</sup> Cahill cites his personal experience in a total of six. All were without symptoms except for pain which was secondary to the large size of the tumor or to metastases. They were found as the result of routine examination, abdominal exploration or autopsy. Perirenal air insufflation aided in the diagnosis of two. On pathologic examination four were carcinomas, one a sarcoma and one an adenoma. Only the latter survived treatment which consisted of transperitoneal excision of the tumor.

Figure 11 is a photomicrograph of a peculiar tumor

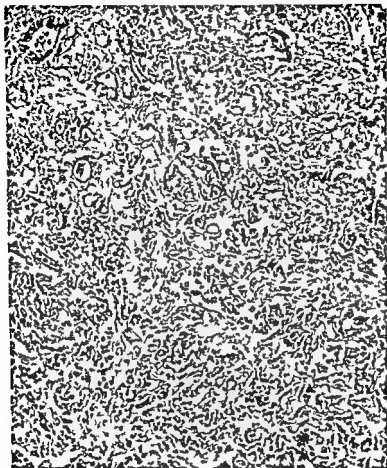


Figure 11 Photomicrograph (x200) of a hormonally inactive cortical tumor found at autopsy

of the right adrenal an incidental finding at autopsy in a 64 year old male who died on the twelfth postoperative day of a massive pulmonary embolus following a simple perineal enucleation of a benign nodular hyperplastic prostate gland (SAR History No 76187 The Johns Hopkins Hospital) Grossly this tumor measured 3 cm

in diameter projected from the surface of the adrenal on section was white and rubbery and possessed a delicate fibrous capsule. The adrenal cortex although thinned out over the tumor was histologically normal. A careful review of the history failed to reveal any signs or symptoms suggesting that this tumor was hormonally active.

### Hormonally Active Cortical Tumors

In certain stages of development nearly all cases of excessive function (hyperadrenocorticism) may be divided into two main groups on the basis of their predominant signs and symptoms. These two groups are 1) the *adrenogenital syndrome* and 2) *Cushing's syndrome*.

Wilkins<sup>14</sup> defines the adrenogenital syndrome as a disorder in which there are evidences of excessive production of adrenal androgen with either (a) no evidence of disturbed cortin production or (b) a deficiency of cortins (corticoids), and Cushing's syndrome as a disorder in which signs of excessive cortin production predominate with usually some evidence of androgen and occasionally increased estrin.

In view of the multiplicity of hormones which the adrenal cortex may produce it is not surprising that a great variety of signs and symptoms may be observed or that there may be gradations between types. By and large the symptom complex observed depends upon the nature of the substance elaborated, the time in development at which this excess function begins and the sex of the patient.

**Cushing's Syndrome** Cushing's syndrome is a term now used by most authors to describe a symptom complex without regard for etiology. The clinical manifestations of this syndrome are identical with those originally described by Cushing<sup>9</sup> found in association with baso-

philic adenomas of the pituitary (Cushings disease or pituitary basophilism) Although the syndrome occurs in young women with greatest frequency men and children of either sex are not immune. Prominent features of the disease are buffalo<sup>1</sup>obesity a term used to describe a characteristic body habitus in which muscular wasting and redistribution of fat leads to apparent obesity of the head and neck and trunk particularly the abdomen while sparing the extremities excessive growth of hair without other evidence of masculinization vascular hypertension diabetes osteoporosis and suppression<sup>2</sup> of sexual function in the form of amenorrhea or impotence. Colorful similes such as moon<sup>3</sup>face pig<sup>4</sup>eye and sun fish<sup>5</sup>mouth have been suggested to describe the facial expressions. Purplish<sup>7</sup>striae may be present over the abdomen. The skin may be atrophic and mottled. Acne may be present. Kyphosis may result from demineralization of the thoracic spine. Polyuria may be a prominent feature.

Examination of the blood may reveal no abnormality. However lymphopenia is nearly always present and erythremia may be. Serum sodium<sup>1</sup>may rise and potassium<sup>4</sup>may fall. Occasionally hypochloremic alkalosis is present with or without change in serum sodium.

The total neutral urinary 17 ketosteroids are often normal but may show moderate to marked<sup>1</sup>increase depending somewhat on the basic cause of the syndrome. These together with values for the so called *beta* fraction will be discussed later. Urinary biocorticoids and chemocorticoids are often increased.

The pathogenesis of Cushings syndrome is most intriguing and the interested reader is referred to the account of the late Edwin J. Kepler<sup>78</sup> who wrote in such a delightful fashion. On theoretical grounds Kepler regarded all cases of Cushings syndrome as a manifesta-

tion of adrenal cortical hyperfunction regardless of anatomic findings and even in the presence of a basophilic pituitary tumor (Cushing's disease) believing that if the adrenal cortices were absent the patient would have few if any symptoms of the syndrome in spite of the fact that his disease continued to be present. On anatomic grounds Kepler presents the probable gross and microscopic findings in a given series of patients with Cushing's syndrome or disease as follows. In almost 100 per cent of cases Crooke's changes will be found in the basophilic cells of the pituitary in only 10 per cent of cases will these be the only findings in the pituitary or adrenal. In approximately 50 per cent of cases a basophilic adenoma of the pituitary will be found. This is usually small and may require serial section to find it may be large and erode the sella turcica. Of those with pituitary tumors one third may have demonstrable hyperplasia of the adrenal cortex. In one in three of the entire series one may find a benign or a malignant adrenal tumor or merely enlarged and presumably hyperplastic adrenal cortices. In some three per cent enlarged adrenals and a thymic tumor may be found and rarely an aberrant adrenal tumor or ovarian tumor.

### **The Diagnosis of Cushing's Syndrome**

**Signs and Symptoms** The appearance of a patient with advanced Cushing's disease is usually so characteristic as to make the diagnosis rather simple. Given an individual with this appearance and in whom several of the prominent features described such as hypertension, diabetes, osteoporosis, etc. are found the diagnosis is established. The cause remains to be determined. At the outset we wish to emphasize that we know of no sure way to determine whether an adrenal tumor or adrenal cortical hyperplasia is responsible for the syndrome.

short of surgical exploration. However, several clinical rules of thumb as well as certain laboratory procedures though not infallible aid in making a preoperative diagnosis.

Generally, patients with all the characteristic features of Cushing's syndrome have adrenal hyperplasia; those with mixed clinical pictures, particularly those with moderate to severe virilization, usually have an adrenal tumor. An enlarged clitoris in an uncomplicated Cushing's syndrome usually speaks for tumor. Female pseudohermaphrodites almost always have congenital adrenal cortical hyperplasia and not tumor. Greatest difficulty arises in determining the cause of simple hirsutism, particularly if associated with obesity, hypertension and menstrual irregularities. Such patients demand a careful diagnostic study.

**Laboratory Aids.** Special laboratory studies in addition to the determination of serum sodium, potassium, chlorides, calcium, phosphorus, carbon dioxide combining power, non-protein nitrogen and glucose include x-rays of the skull, long bones and thoracolumbar spine; intravenous (and at times retrograde) pyelograms; perirenal insufflation of air; aortograms; laminograms; and the determination of urinary 17 ketosteroids (including *alpha* and *beta* fractions), 11 oxysteroids (corticoids) and urinary estrogens or estrogens.

Provided an adrenal tumor is large, pyelograms may show downward displacement of the kidney. In the hands of those experienced with the method (Cahill<sup>13</sup>, Roome<sup>14</sup>, Mencher<sup>15</sup> and Vest<sup>16</sup>), perirenal air insufflation films have been useful and without complications or fatalities.

Recently several clinicians have advocated perirenal and extraperitoneal pneumography via the paracostal route.<sup>17</sup> There follows a brief description of the technique used by Stembich *et al.*<sup>17</sup>



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Recently several clinicians have advocated perirenal and extraperitoneal pneumography via the paracoccygeal route.<sup>17, 18</sup> There follows a brief description of the technique used by Steinbach *et al.*<sup>17</sup>

With the patient in the side position legs drawn up the anus is anesthetized with anesthetic ointment the injection site prepared with antiseptic solution and procaine injected in the midline between anus and coccyx 1.2 cm from the latter. A No. 18 or 19 spinal needle is inserted through skin and subcutaneous tissue until the tip impinges on the tip of the coccyx. The index finger of the free hand is placed in the rectum and the needle is re-directed to slide along the anterior surface of the coccyx and through the anococcygeal raphe (Figures 12A and B). The needle is inserted another 2-3 cm care being taken to avoid injury to the rectum. A few cubic centimeters of air is inserted to check the position. The injection set consisting of a bottle of oxygen and a bottle of water is attached to the needle through a sterile section of rubber tubing (Figure 12C). The oxygen is allowed to flow in at a pressure of 15-20 cm water. The volume of oxygen needed varies with the patient. About 15 cc/kg body weight of oxygen is enough to visualize both sides of the body. If an extraperitoneal pneumogram of a single side of the body is required that side is kept in the superior position since the oxygen rises to the highest portion of the extraperitoneal tissue. If a generalized pneumogram is desired half the gas is injected with one side elevated and half with the other side elevated.

"X rays can be taken as soon as the injection is com-

pleted. optimal time is two hours after injection.

In our experience several tumors have been visualized on laminograms and aortograms (*Vide infra*).

Estimation of the levels of certain urinary steroids is of distinct value in the differential diagnosis of adrenal hyperplasia and tumor. In this regard the interested reader is referred to the writings of Mason and Engstrom<sup>31</sup> Munson *et al*<sup>32</sup> Forbes and Albright<sup>33</sup> Gardner and Migeon<sup>34</sup> and Lindau<sup>35</sup>. A few salient points follow

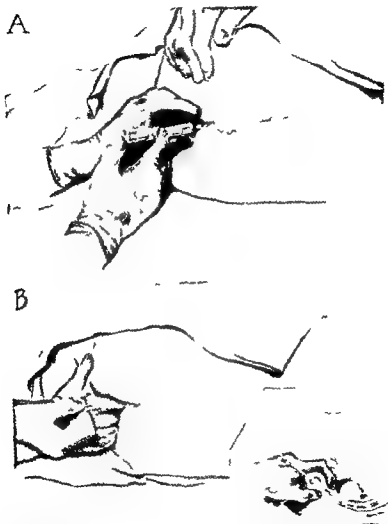


Figure 12 A and B The spinal needle is first inserted until the tip impinges upon the tip of the coccyx. The index finger of the opposite hand is placed in the rectum and the needle is redirected so as to slide along the anterior surface of the coccyx and through the anococcygeal raphe

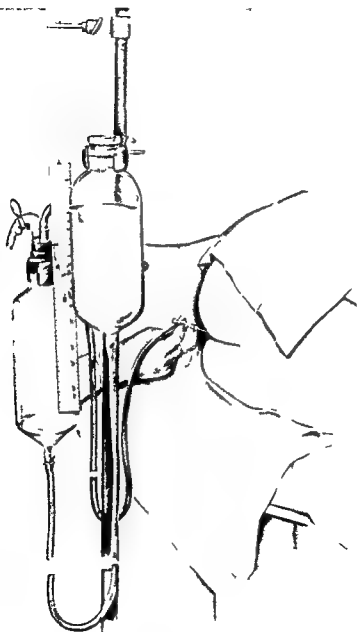


Figure 12 C (*See legend on opposite page* )

Adrenal cortical tumors are often associated with an increase in urinary 17 ketosteroids. Mason and Engstrom<sup>91</sup> found only two exceptions to this in a review of 50 cases in the literature and in these two poor preservation of the urine and extreme illness respectively may well have been responsible. Not included in this survey were two others recently studied by Mason who also had normal values. In one evidence of increased cortical function was found in an increased excretion of corticosteroids.

Forbes and Albright<sup>40</sup> in a recent review of 90 cases of Cushing's syndrome in whom the adrenals were visualized and classified according to pathologic change found the average 17 ketosteroid excretion to be "without tumor 18.1 with benign tumor 5.7 and with malignant tumor 124.4 mg per 24 hours."

Whereas total urinary 17 ketosteroids may be elevated in adrenal hyperplasia as a rule they are not as high as in cases of adrenal tumor. Furthermore although no 17 ketosteroid has been found which is characteristic of either condition the *beta* fraction is more frequently elevated in cases of tumor and dehydroisoandrosterone is more readily isolated.\* In this regard Mason and Engstrom<sup>91</sup> sum up the available data as follows. Thus data now available suggests that a daily excretion of more than 50 mg of 17 ketosteroids 50 per cent or more of which is *beta* fraction indicates the presence of an adrenal cortical tumor. Fine distinctions and sharp lines of demarcation cannot be made.

Pregnactriol (pregnane 3 (*alpha*) 17 20 triol) has been isolated from the urine of seven cases of adrenal hyperplasia and in one case in which a clinical diagnosis of an adrenal cortical tumor was made. Unfortunately in the latter instance the diagnosis of tumor was not confirmed by laparotomy or autopsy.<sup>92</sup>

←  
Figure 12 C The injection set up is attached to the needle through a sterile section of rubber tubing and a cotton filter. Oxygen is allowed to flow in at a pressure of 15 to 20 cm. of water.

Recent studies by Gardner and Migeon<sup>4</sup> working in Wilkins laboratory have a distinct bearing on the problem. Using a color test for dehydroisandrosterone like compounds initially suggested by Dirscherl and Zilliken<sup>31</sup> and developed by Allen *et al* they were able to confirm the latter's findings of positive tests in adrenal cortical tumor patients but not in adrenal hyperplasia although total 17 ketosteroids were high in both groups and the results of *beta* separation with digitonin were equivocal. Furthermore when cortisone was given urinary 17 keto steroids were reduced to normal values in children with hyperplasia (two cases) but not in cases of adrenal cortical tumor in children (two cases).

Lastly Wilkins<sup>34b</sup> has found the determination of neutral reducing lipids of the urine (formerly called 11 oxysteroids) to be of some diagnostic importance. He lists the following values: children—0.3 to 0.6 mg per 24 hours; adults—0.5 to 1.0; adrenogenital syndrome—0.5 to 2.0; and Cushing's syndrome—2.0 to 5.0.

### Cushing's Syndrome in Children

In his masterful treatise on endocrine disorders in childhood Wilkins<sup>34c</sup> reviews the reported cases of Cushing's syndrome in children listing 26 under the age of 10 years. All in this group had tumors! After the age of 10 the syndrome was found in association with adrenal tumor, adrenal hyperplasia or a basophilic adenoma of the pituitary. By and large the symptom complex in children is similar to that seen in the adult. To illustrate the salient features the following case is presented in detail.

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As always nothing is 100 per cent. In an article which appeared after Wilkins' book Albright and associates<sup>35</sup> state: "The only patient with Cushing's syndrome due to adrenal hyperplasia which the authors have been able to find was an eight year-old girl. However, they do maintain that Adrenal tumor is the only cause of Cushing's syndrome recorded in infants and small children."

This female infant in addition to Cushing's syndrome showed moderately severe masculinization as evidenced by marked hirsutism and moderate enlargement of the clitoris

G F History No A 55822 Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital born January 28 1947 was seen in the pediatric endocrine clinic The Johns Hopkins Hospital by Dr Lawson Wilkins on July 12 1947 at the age of 5½ months At three months of age the parents noted that her cheeks were fat and that she was developing acne of her face and scalp Several weeks later hair was noted on the upper lip followed in several weeks by the appearance of hair in the region of the genitals A gradual enlargement of the abdomen was observed over the course of several months and vocal utterances were observed to be somewhat deep Dr Wilkins description of body build and proportions skin hair and sexual development are classic and are as follows

This baby is of average size for her age and has normal skeletal proportions She presents a very striking appearance because of her marked obesity Although she is only 3 lbs above the average weight she presents a characteristic buffalo type of obesity There is a huge fat face with bulging cheeks between which there is a tiny stubby nose Cheeks and chin are so fat as to almost hide her neck There is immense padding of fat over her shoulder upper back and chest The abdomen is distended and somewhat obese The legs although fat are much less so than the upper trunk and face (Figure 13)

Her face is very red There is marked acneiform eruption consisting of pustules and papules over the forehead cheeks and extending up into the scalp Skin in this region seems very oily and her scalp and hair are oily There is no acne lesion on the body

"She has abundant black hair on the scalp which grows down low on her forehead almost to her eyebrows Eye



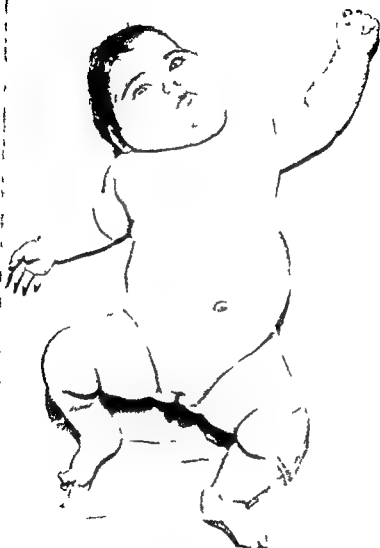


Figure 13 Cushing's syndrome associated with an adrenal cortical carcinoma in a female age five months. Normal growth until birth. Characteristic facies of two months duration. Blood pressure 180/110 to 210/120. Total 17 ketosteroids 77 mg. per day. Mildly diabetic glucose tolerance curve. Large mass in region of right

brows are thick and black almost meeting in the mid line There is fine black down on her upper lip some on the upper chin and fine sideburns extend down on her cheeks There is a heavy growth of long fine black hair over her back especially in the upper region There is some coarse black hair on the labia and a little fine black hair in the axilla

Her cry is rather deep and hoarse The areolar measure about 1 cm in diameter and are somewhat brownish The nipples are undeveloped and no mammary tissue is palpable The labia majora are greatly hypertrophied and show marked pigmentation There is a moderate growth of coarse dark hair 2 to 3 cm in length on the labia The clitoris is considerably enlarged measures 2 cm in length is much thicker than the average with plainly visible glans and hypertrophied preputial folds and shows a tendency to erections The labia minora are entirely infertile and undeveloped There is distinctly separate urethral and vaginal orifice of normal infantile configuration

General examination revealed a palpable mass in the right upper quadrant and flank which was felt to represent a normal kidney displaced downward medially and anteriorly by a retroperitoneal mass The blood pressure on several examinations ranged from 180/120 to 210/110

Laboratory data revealed the following abnormal findings A moderate polycythemia a moderate leucocytosis a mild diabetic glucose tolerance curve and 77 mg total neutral urinary 17 ketosteroids per 24 hours An intravenous pyelogram was unsatisfactory However retrograde pyelograms revealed a normal left kidney and a normal right kidney displaced downward and anteriorly by a large right upper quadrant mass The initial chest

**Adrenal treatment**

**NAP**

**Elixir sodium**

**NAP**

**NATIO**

normal on pyelogram Child died six months after operation Blood urea and 17 ketosteroids falling after operation returned to normal high levels prior to death (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital)

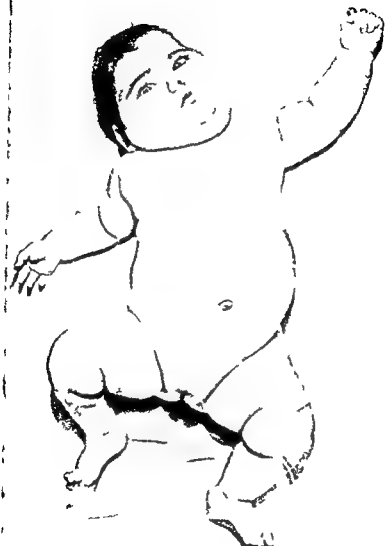


Figure 13 Cushing's syndrome associated with an adrenal cortical carcinoma in a female age five months. Normal genitalia at birth. Characteristic facies of two months duration. Blood pressure 180/110 to 210/120. Total 17 ketosteroids 77 mg. per day. Mildly diabetic glucose tolerance curve. Large mass in region of right

Prior to operation the infant received 3000 roentgen units measured in air (5 x 200 anteriorly and 10 x 300 posteriorly over the tumor area) without apparent effect on the size of the tumor. Of considerable interest was the observation that on the day prior to x-ray therapy she excreted 55.1 mg. total neutral urinary 17 ketosteroids per 24 hours and immediately after cessation of the 15 treatments described 105.3 mg. per day.

On July 24, 1947, excision of an adrenal tumor was carried out through a right upper abdominal transverse incision extending from the left of the midline laterally into the right flank. No metastases could be found in the abdomen. Special pre and postoperative therapy, so important in all adrenal surgery, was carried out and the patient made an uneventful recovery. In that this varied but little from an established routine to be described subsequently, it is not presented separately.

Grossly the tumor was well encapsulated and weighed 250 grams. Histologically: (Figure 14) the tumor resembled closely adrenal cortex and adrenal carcinoma (hypernephroma) being made up of clear cells with dark staining nuclei. An abundance of lipid within these cells was evident on fat stain. Histologically it was not possible to tell whether or not the tumor was malignant and the final pathologic diagnosis was adrenal cortical tumor.

Following section 250 grams of tumor were extracted with carbon tetrachloride and after appropriate separation a Zimmermann reaction run (Dr. Roger Lewis). This revealed 36 mg. of 17 ketosteroid in the entire tumor. Ten days postoperatively urinary 17 ketosteroids had risen to 67.4 mg. per 24 hours. On November 23, 1947, four months after operation the infant expired. Autopsy was refused.

## **The Treatment of Cushing's Syndrome**

**Surgical.** Since it is not possible to determine with certainty the cause of Cushing's syndrome in explora-

x ray was read as normal and x rays of the long bones showed approximately normal osseous development

A diagnosis of an "adrenal tumor manifesting evidence of excessive secretion of both corticoids and androgen was made. Normal configuration of the urethra and vagina excluded the possibility of congenital adrenal hyperplasia and female pseudohermaphroditism



Figure 14 Photomicrograph (x75) of an adrenal cortical carcinoma causing Cushing's syndrome in the female infant shown in Figure 13

taken by mouth. Four grams of salt daily should be added to the diet. Shortly all special therapy can be discontinued. As in cases of operative removal of pheochromocytomas (which see) postoperative hypotension can be combatted with a continuous infusion of dilute epinephrine, norepinephrine or neosynephrine.

**Subtotal Adrenalectomy** In those cases of Cushing's syndrome in which a tumor is not found generally in the past treatment has been unsatisfactory. If caused by a basophilic adenoma of the pituitary or adrenal cortical hyperplasia other methods have been used. These have included pituitary irradiation in an effort to inhibit the production of ACTH androgen administration for its protein anabolic action as well as its reparative effect on bone matrix, estrogen administration (usually with androgen) to increase calcification and subtotal and total adrenalectomy in an effort to overcome hyperfunction of the adrenal cortex. Improvement has been reported after these various forms of treatment but it is difficult to assess because of spontaneous variations in the course of the disease. For a splendid discussion of the natural history of Cushing's syndrome the reader is referred to a recent article with this title by Plotz *et al*<sup>103</sup>. Until recently little data were available to aid in assessing the value of subtotal adrenalectomy.

Our own experience does not permit us to discuss subtotal adrenalectomy for Cushing's syndrome intelligently but we wish to refer to a comprehensive article on the subject by Priestley *et al*<sup>111</sup> as well as a previous communication by E. J. Kepler.<sup>6</sup> The summary of the article by Priestley and his associates is quoted in extenso: "Extensive bilateral subtotal adrenalectomy has been performed in 29 cases of Cushing's syndrome in which surgical exploration failed to reveal a functioning adrenal cortical tumor. There were six postoperative deaths, all

tion of both adrenals should always be performed. If a cortical adenoma or localized cortical carcinoma is found surgical excision offers a good chance for cure. Preferred surgical routes for various types of adrenal cortical and medullary tumors will be presented subsequently.

According to most observers functioning cortical tumors resulting in Cushing's syndrome are almost always associated with some degree of atrophy of the contralateral adrenal. Consequently strict attention must be given to proper supportive therapy. Since the advent of cortisone management has been much less of a problem. Whereas it is impossible to set forth a rigid system of management certain suggestions may be made regarding the administration of adrenal hormones, electrolytes, glucose and fluid.

In adults with Cushing's syndrome in whom a unilateral tumor has been demonstrated preoperatively or in those in whom it is felt that a tumor is most likely present we recommend the following substitution therapy.

The night before the operation the patient is given 50 mg. cortisone acetate, 3 mg. desoxycorticosterone acetate (DCA) and 5 grams of salt. Just prior to surgery 100 mg. cortisone acetate and 5 mg. DCA are given parenterally. During operation 1000 cc. of 5 per cent glucose is given intravenously and whole blood if necessary. This is followed by 500 cc. of 5 per cent glucose in normal saline. For the first 24 hours additional fluid in the form of 5 per cent glucose is injected to make a total of 3000 cc. Cortisone acetate 50 mg. every four to six hours completes substitution therapy for the day of operation. During the succeeding 24 hours 3000 cc. of 5 per cent glucose is given intravenously, one sixth of which is in normal saline. Cortisone acetate 50 mg. every six hours is continued and one dose of 3 mg. DCA is given. Usually within 72 hours after operation the amount of cortisone can be reduced appreciably. DCA stopped altogether and fluids can be

satisfactory remission regrowth may lead to relapse resection of too much tissue leads to adrenal insufficiency requiring replacement therapy which in itself must be balanced nicely Indeed the situation is somewhat analogous to surgical therapy for hyperthyroidism and based on this analogy one might predict that results following subtotal adrenalectomy will improve And too as more is learned of the original cause of adrenal hyperfunction greater efforts will be made to find suitable analogs which may obviate surgical maneuvers

Recently several clinicians have suggested total adrenalectomy for Cushing's syndrome

**Resume of Surgical Treatment** In an attempt to clarify the approach to the surgical management of Cushing's syndrome Sprague *et al*<sup>1,6</sup> and Albright and his associates<sup>41</sup> quite independently have drawn up a formula to follow By and large we agree

1 If the first adrenal gland explored is atrophic almost surely the contralateral gland is involved in tumor

2 If the first adrenal gland explored is large the patient has adrenal hyperplasia and the contralateral gland will be large also

3 If the first adrenal gland explored is normal in size this adrenal and its opposite are probably hyperfunctioning though not hyperplastic and a contralateral tumor is unlikely

In situation 1 as outlined previously removal of the tumor constitutes therapy In so doing the need for replacement therapy is paramount in situations 2 and 3 subtotal adrenalectomy appears to be the procedure of choice at present of those with the most experience

**Virilizing Tumors** Adrenal cortical hyperplasia and adrenal cortical tumors may cause virilization rapid



of which occurred prior to the use of cortisone in both the preoperative and postoperative management. Of the 23 remaining patients one patient experienced no improvement following operation three patients will require further observation as the postoperative period has been too short to allow evaluation of the results and 19 patients have obtained an excellent remission of the Cushing's syndrome. However three of the 19 patients have adrenal insufficiency. In general the results have been encouraging and appear to support the concept that regardless of what the primary etiology of the syndrome may ultimately prove to be its features are contingent upon hyperfunction of the adrenal cortices. It appears entirely possible that results may be improved in the future.\*

Certainly this work emphasizes the importance of the adrenal cortex in the pathogenesis of Cushing's syndrome as well as the advantage of cortisone over adrenal cortical extracts in the postoperative management of these patients. It also points up the nicety of balance which apparently must be achieved in order to provide a continuous remission. Resection of insufficient adrenal cortex results in failure; resection of sufficient tissue leads to

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After completion of this monograph an article by Sprague Kvale and Priestley<sup>28</sup> appeared in which they add 21 cases bringing their total to 50. In their last 27 consecutive cases there has been only one postoperative death and much of their success they attribute to judicious use of cortisone and desoxycorticosterone acetate. Of a total of 41 patients now living 40 are judged to be in a state of satisfactory remission. Of these 20 require replacement therapy in the form of cortisone given orally and 10 of these 20 require in addition desoxycorticosterone acetate given buccally. Length of remission has ranged from three months to seven years. Several have had a second remission after relapse upon resection of more adrenal tissue. This has prompted the authors to state: "Since it must be presumed that the original adrenal cortical hyperfunction continues to act after a remission has been induced by removal of adrenal tissue additional recurrences can be anticipated with the passage of more time."

satisfactory remission regrowth may lead to relapse resection of too much tissue leads to adrenal insufficiency requiring replacement therapy which in itself must be balanced nicely. Indeed the situation is somewhat analogous to surgical therapy for hyperthyroidism and based on this analogy one might predict that results following subtotal adrenalectomy will improve. And too as more is learned of the original cause of adrenal hyperfunction greater efforts will be made to find suitable analogs which may obviate surgical maneuvers.

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In situation 1 as outlined previously removal of the tumor constitutes therapy. In so doing the need for replacement therapy is paramount. In situations 2 and 3 subtotal adrenalectomy appears to be the procedure of choice at present of those with the most experience.

**Virilizing Tumors** Adrenal cortical hyperplasia and adrenal cortical tumors may cause virilization rapid

growth increased muscularity and accelerated epiphyseal ossification (androgenic effects) and yet be unassociated with signs suggesting hypersecretion of corticoids as seen in Cushing's syndrome. Such a syndrome has been called adrenal virilism, interrenalism and the adrenogenital syndrome, the latter preferred by most.

As indicated heretofore the clinical picture observed depends upon the time in development at which excess androgen production occurs and the sex of the patient. If adrenal hyperplasia occurs before intrauterine differentiation of the sex organs, the resulting abnormality will be either macrogenitosomia precox (congenital adrenal hyperplasia) in the male or pseud hermaphroditism in the female. If either adrenal hyperplasia or cortical tumor develops after differentiation of the sex organs, the result may be virilization in the female, both in the child and the adult, and precocious sexual development in the male child.

### **In the Female Child**

**Incidence.** To 1948 Wilkins<sup>143</sup> found reports in the literature of 70 cases of adrenal cortical tumors in children. Of these 53 were girls, 31 with signs and symptoms of uncomplicated adrenogenital syndrome and 22 with findings suggesting Cushing's syndrome. He concluded that "From the time of birth until the tenth or twelfth year virilization is usually, if not always, due to adrenal tumor. After this age virilization may be due to either tumor or hyperplasia."

**Diagnosis.** In contrast to a female pseud hermaphrodite with congenital adrenal hyperplasia at birth, a female child with a virilizing tumor has no malformation of the genitourinary apparatus. Unlike the female pseud hermaphrodite who shows a urogenital sinus (Figure 15), the female infant with tumor has a normally situated

urethral orifice which is separate and distinct from the vagina and normal infantile female genitalia. Virilization secondary to tumor has been observed as early as the third month of life. Once in progress development may be quite rapid.



FIGURE 15. Simultaneous demonstration of urogenital sinus vagina and urinary bladder by x ray following the injection of a radio-opaque liquid

We have chosen to illustrate the progress of events in these cases by presenting a representative case

J C History No A 33040 Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital a female age 5½ years was admitted in 1943 to the Endocrine Serv

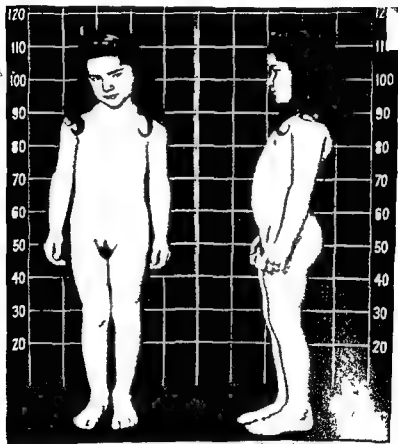


Figure 16 A Virilization in a young girl/secondary to an adrenal cortical carcinoma A appearance of the patient five months after onset of symptoms and before operation B one year later Reoperation disclosed recurrent tumor (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital J Clin Endocrinol 8 111 1948)

ice of Dr Lawson Wilkins Six months before the mother had noticed that the clitoris was a little prominent and since had become progressively larger Shortly thereafter pubic hair appeared and continued to grow The voice became deep Although she gained weight rather rapidly

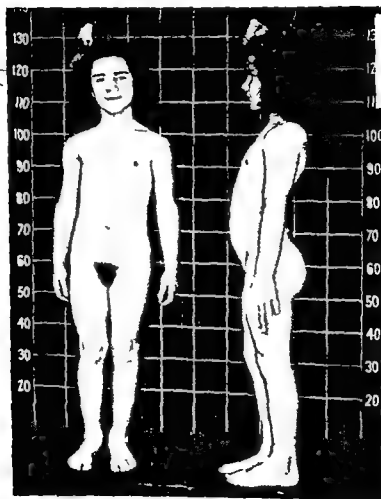


Figure 16B (See legend on opposite page)  
Died 2 1/2 yrs after onset of disease  
& 2 yrs after removal of tumor

she did not become obese. The skin became oily and a slight eruption appeared. On examination some acne of the face was seen but no unusual amount of facial hair. Muscular development seemed advanced. Breasts and nipples were infantile and there was no axillary hair. Pubic hair was abundant (Figure 16A) and the labia majora and clitoris were markedly enlarged. Urethral and vaginal orifices were normally situated. On pelvic examination under anesthesia both ovaries and uterus were slightly smaller than for the average child of five years. X rays revealed a bone age of seven years, a normal sella turcica and normally situated kidneys. Values for total 17 ketosteroids ranged from 19 to 22 mg per day, the beta fraction constituting less than 1 per cent of the total. At operation through a transverse upper abdominal incision a golf ball sized tumor was found springing from the right adrenal. This was removed. The left adrenal appeared normal. Figure 17 shows the microscopic appearance of the tumor which at operation appeared well encapsulated and was described as an adrenal cortical adenoma. Except for 10 mg of DCA given prior to operation no hormonal therapy was used. Her postoperative convalescence was uneventful and she was discharged from the hospital. Within four months the 17 ketosteroids had fallen to 2.1 mg per day. However there was no regression of pubic hair (Figure 16B) and the clitoris remained large. Within one year after operation the 17 ketosteroids had increased to 94 mg per day and reoperation revealed multiple recurrences of the tumor in the mesentery. Within another year the patient expired, approximately two years after removal of the original tumor. The last 17 ketosteroid determination prior to death showed an excretion of 124 mg per day.

Several points are worthy of comment. In the differential diagnosis congenital adrenal hyperplasia was excluded on the bases of absence of a urogenital sinus and other defects characteristic of female pseudohermaphro-

ditism - premature pubarche was excluded by the observations that virilization was progressive the clitoris was enlarged and 17 ketosteroids were abnormally high. Recurrence of tumor was predicted by the return of high levels of excretion of total urinary 17 ketosteroids. Cortical carcinomas are frequently distinguished from cortical adenomas primarily on histologic evidence of invasion (absent here) and clinical evidence of metastasis (present one year before death).

**Treatment** Provided there is no clinical evidence of metastases surgical excision provides the only cures. Often these tumors are malignant metastasizing to the lungs liver and skeleton. In cases where the diagnosis is in question early exploration is indicated.

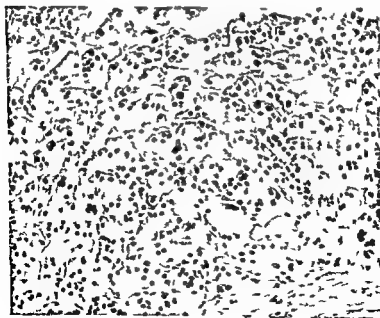


Figure 17 - Photomicrograph ( $\times 200$ ) of adrenal cortical carcinoma causing virilization of young girl shown in Figures 16 A and B



### In the Male Child

**Incidence** In Wilkins study of 70 tumors in children described in part above 17 were boys. Of these 12 presented a clinical picture consistent with the diagnosis of adrenogenital syndrome. Two showed obesity of the Cushing's type. One was feminized and will be described below under the heading *Feminizing Tumors*.

Since this review several additional cases have been reported and others observed including one unreported case seen by us which will be used herein as an illustration of a representative case.

**Diagnosis** One suspects an adrenal cortical tumor in a male child if sexual precocity occurs. However early virilization may be secondary to congenital adrenal hyperplasia or an interstitial cell tumor of the testis.

Whereas it may be impossible short of surgical exploration to differentiate tumor from congenital hyperplasia several features of the latter may help. A familial history of either male or female hyperplasia strongly suggests hyperplasia as does any evidence of adrenal insufficiency such as Addisonian pigmentation. Total 17 ketosteroids and particularly the *beta* fraction are usually lower.

An interstitial cell tumor of the testis may at times be palpable. In questionable cases testicular biopsy is indicated.

Again we have chosen to illustrate the main features in the diagnosis by example.

**H. B. History No. A 94056** Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital. A boy aged four years and nine months was admitted in 1951 to the Endocrine Service of Dr. Lawson Wilkins and subsequently seen in consultation by one of us. Two years before the child's parents had noted enlargement of the

penis and the appearance of pubic hair. Shortly thereafter he was studied at Duke University Hospital where it was recorded that the penis was markedly enlarged, sparse pubic hair was present, height age was 4½ years, x-rays of the bones showed accelerated ossification, pyelograms showed the presence of a mass in the left upper quadrant which depressed the left kidney, a test for urinary gonadotropins was negative and total urinary 17 ketosteroids ranged from 73 to 144 mg per day, 50 to 60 per cent representing the *beta* fraction. A diagnosis of "adrenal cortical tumor" was made but operation was refused. He returned home and during the two succeeding years the parents noted progressive enlargement of the penis, the increase in pubic hair and deepening of the voice. He had become very muscular and stronger than his brother who was two years his senior. On initial examination here his height age was eight years and his bone age 12 years. There was marked development of male secondary sexual characteristics (Figure 18 A) with pubic and axillary hair, deep voice, advanced adolescent development of penis, scrotum and prostate, but no apparent adolescent development of the testes, the size of which were within normal limits for his age. The blood pressure varied between 104/54 and 112/72. Urinary 17 ketosteroids ranged from 106 to 194 mg per day, and the color test for dehydroisoandrosterone was strongly positive. An intravenous pyelogram (Figure 18 B) showed downward displacement and rotation of the left kidney, apparently due to a mass above it. Percutaneous aortograms were not diagnostic. Blood chemistries including serum electrolytes and glucose tolerance were normal. A transthoracic operation removed an encapsulated 7 cm adrenal tumor (Figure 18 C) which on section (Figure 18 D) was judged to have arisen from the cortex. The postoperative course was uneventful and no hormonal therapy was required. The patient has remained well to date and continues to show regression of precocious sexual characteristics.

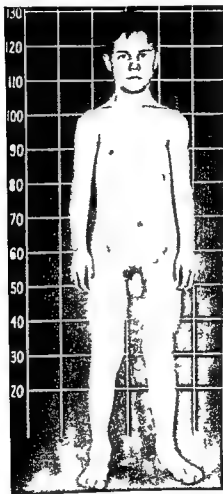


Figure 18 A Virilization associated  
with an adrenal cortical tumor  
has remained well 3 yrs  
after removal of tumor

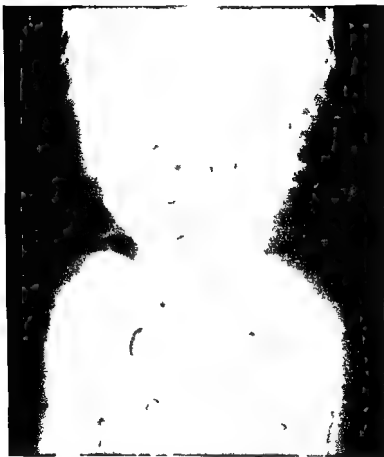


Figure 18 B Intravenous pyelogram showing downward displacement and rotation of the left kidney by the tumor

Here the preoperative diagnosis of a virilizing adrenal cortical tumor was almost certain. Masculinization was plainly evident; there was no history of congenital adrenal hyperplasia in siblings; adrenal insufficiency was not apparent and blood chemistries were normal. The kidney was displaced by a probable tumor mass and both total and *beta* 17 ketosteroids were markedly increased. The

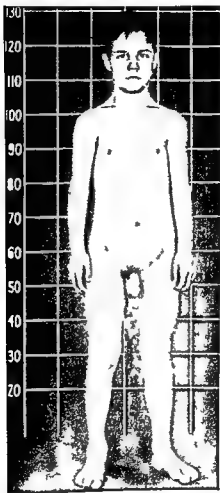


Figure 18 A Virilization associated with an adrenal cortical tumor has remained well 3 yrs after removal of tumor

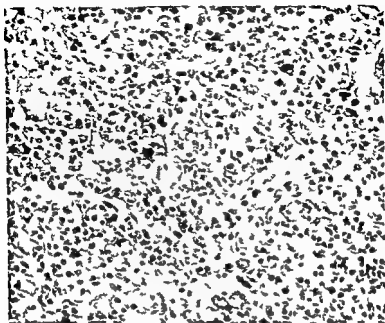


Figure 18 D Photomicrograph (x200) of the tumor

Kepler and Keating, Cahill and his associates<sup>9, 10</sup>, Walters and Sprague<sup>14</sup> and Cleroux and Oppenheim<sup>15</sup> have added a number of cases in which a picture of an complicated adrenogenital syndrome in adult women has been associated with an adrenal cortical tumor. We have not attempted a review and tabulation of all published cases.

**Diagnosis.** Masculinization without the metabolic symptoms usually seen in Cushing's syndrome may occur in adult women as the result of adrenal cortical hyperfunction: arrhenoblastomas of the ovary or after prolonged administration of large amounts of androgen (Figure 19 A and B). Adrenal cortical hyperfunction may occur in conjunction with tumor.

Arrhenoblastomas of the ovary may be palpable on



Figure 18 C The tumor in the gross

testes were preadolescent in size and no tumor was palpable within either

**Treatment** : Surgical excision : Routes will be discussed below

### **In the Adult Female**

**Incidence** In a review of the literature prior to 1937 Hugh Young<sup>1</sup> found reports of 24 cases of adrenal cortical tumor in females over the age of 16 years in which surgical excision of the tumor had been performed. Unfortunately the histories lacked sufficient detail to permit him to sort them into distinct categories although all were described under the heading "The Adreno Cortical Syndrome." A number most certainly would now be classified as examples of Cushing's syndrome.

Since Young's review a number of authors including

pelvic examination but when not may confuse the diagnosis. Like cases of pure adrenogenital syndrome arrhenoblastomas are almost never associated with the metabolic symptoms usually seen in Cushing's syndrome.

As Kepler and Locke<sup>78</sup> have pointed out "pseudo adrenal and quasiadrenal disorders often are the cause of diagnostic worries. Simple hirsutism rarely proves to be secondary to an adrenal cortical tumor but when it is associated with obesity and amenorrhea and at times with mild virilism great difficulty may be encountered in establishing the diagnosis. All the tools of the endocrinologist may be needed to solve the riddle; the true diagnosis may not be established prior to surgical exploration and at times not then even though sections of the adrenal are studied.

The following case serves to illustrate the principal diagnostic features of the adrenogenital syndrome in an adult female resulting from an adrenal cortical carcinoma.

B C History No 457100 The Johns Hopkins Hospital a female age 27 years was admitted to the Surgical Service of Dr Mark Ravitch in 1948 complaining of left upper quadrant pain amenorrhea the appearance and growth of hair over the face abdomen and extremities huskiness of voice and a 30 to 40 pound weight loss all of approximately eight months duration. Examination revealed a slender woman showing male distribution of pubic and abdominal hair a definite beard a husky voice a small goiter and a large hard rounded left upper quadrant mass. The ovaries felt normal on pelvic examination. Pycnograms made elsewhere showed a normal left upper urinary tract except for downward displacement of the entire kidney by an extrarenal mass. This mass also caused medial displacement of the stomach. Chest x rays were negative. Blood studies were within normal range. Total urinary 17 ketosteroids were 69.3 mg per day the beta fraction was not determined. Abdominal exploration



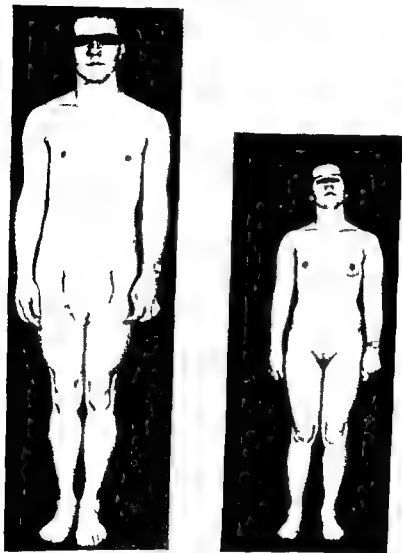


Figure 19 A and B A (Left) preoperative appearance of an 18-year-old female with adrenogenital syndrome caused by an adrenal cortical adenoma; B (Right) appearance of patient seven months after removal of the tumor (Courtesy of Dr John F. Howard, The Johns Hopkins Hospital)

showed downward displacement of the left kidney the total urinary 17 ketosteroids were markedly elevated and the ovaries felt normal. There were no metabolic symptoms suggestive of Cushing's syndrome and blood studies were normal.

**Treatment**—Provided there is no evidence of metastases surgical excision of the tumor constitutes proper treatment as it does in all cases of adrenal tumor regardless of what type of symptoms are produced.

### **Feminizing Tumors**

Hyperadrenocorticism in the male secondary to tumor usually results in Cushing's syndrome. Occasionally, however, isolated expressions of hyperfunction such as feminization may occur without metabolic symptoms.

### **In the Male Child**

The only case of an adrenal cortical tumor causing gynecomastia in a male child prior to puberty is that reported by Wilkins<sup>14</sup> some details of which are presented below. It will be noted that there is little in the history and examination to suggest feminization other than the pronounced gynecomastia. In discussing this case Wilkins points out that gynecomastia is rare between the neonatal period and adolescence and when present suggests a feminizing adrenal tumor. In the newborn gynecomastia may result from circulating estrogens produced by the mother and after puberty may be associated with adrenal tumors, testicular chorioepitheliomas, liver disease, Klinefelter's syndrome and following feeding after a period of severe inanition.

■ G History No A-31153 Hurmet Iunc Home for Invalid Children of The Johns Hopkins Hospital a boy aged four years and eight months was admitted in 1943 to the Endocrine Service of Dr. Lawson Wilkins. Dr. John

was carried out through a long transverse upper abdominal incision which transected both recti. Exposure and removal of a huge 1160 gram tumor was facilitated by resection of three costal cartilages. Fifty cubic centimeters of adrenal cortical extract and 5 units of blood were given during operation. Postoperative recovery was prompt. The tumor on section was an adrenal cortical carcinoma (Figure 20). When last seen in July 1949 15 months after operation her menstrual periods were regular and there was little external evidence of masculinization. Her voice was soft and feminine. Unfortunately 17 ketosteroid determinations were not repeated.

Here again the preoperative diagnosis of a virilizing adrenal cortical tumor was almost certain. Masculinization was of recent onset and progressive. The pyelograms

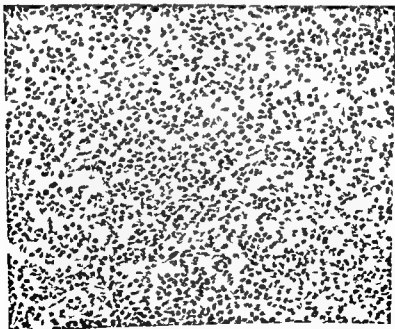


Figure 20 Photomicrograph (x200) of an adrenal cortical carcinoma associated with virilization of an adult female

showed downward displacement of the left kidney the total urinary 17 ketosteroids were markedly elevated and the ovaries felt normal. There were no metabolic symptoms suggestive of Cushing's syndrome and blood studies were normal.

**Treatment.** Provided there is no evidence of metastases surgical excision of the tumor constitutes proper treatment as it does in all cases of adrenal tumor regardless of what type of symptoms are produced.

### **Feminizing Tumors**

Hyperadrenocorticism in the male secondary to tumor usually results in Cushing's syndrome. Occasionally however isolated expressions of hyperfunction such as feminization may occur without metabolic symptoms.

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D. G. History No. A-31153. Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital: a boy aged four years and eight months was admitted in 1943 to the Endocrine Service of Dr. Lawson Wilkins. Dr. John

Eager Howard had been asked to see the boy previously in the Accident Room because of enlarged breasts. Questioning of the mother revealed that she had noted that the boy's breasts first began to enlarge at the age of six months. Neonatal hyperplasia of the breasts had not been observed. Nothing else unusual had been noted by the mother and growth and development had appeared normal to her. His appearance on examination is shown in Figure 21 A. Positive findings were a bone age of 10

Age 4 yr  
8 mos  
normal  
breast lobes in  
this child  
higher  
more than  
normal

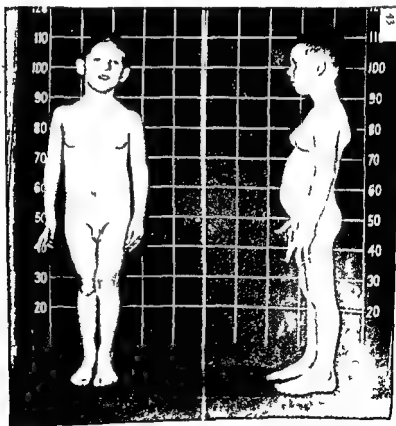


Figure 21 A Feminization associated with an adrenal cortical tumor prior to removal (Courtesy of Dr Lawson Wilkins, The Johns Hopkins Hospital)

years marked mammary development some enlargement of the prostate calcification in the region of the right adrenal above a bifid right kidney (Figure 21 C) a slight eosinophilia and a total urinary 17 ketosteroid excretion of 41 mg per day Urinary estrogens were slightly increased On exploring the abdomen through a trans

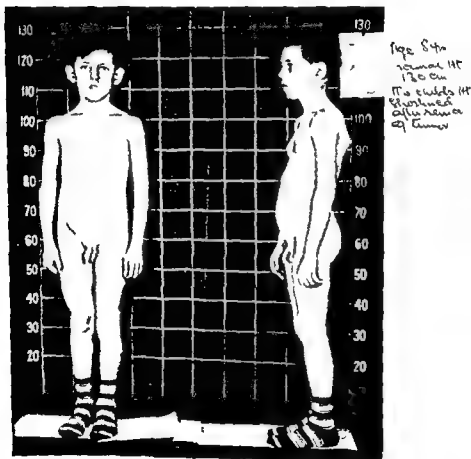


Figure 21 B Appearance of patient three years and three months later (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital)



Figure 21 C Intravenous pyelogram showing area of calcification in the tumor above but not displacing a bifid right kidney (Courtesy of Dr. Lawson Wilkins, The Johns Hopkins Hospital)

verse upper abdominal incision, an encapsulated calcified peanut-sized tumor could be seen springing from the right adrenal. Both the tumor and the right adrenal were removed. The left adrenal appeared normal. On microscopic examination the tumor appeared to be a benign cortical adenoma, thought possibly to arise from the pre-

renal zone (Figure 21 D) The only hormonal therapy used was 10 mg. DCA on the day of operation and his postoperative course was quite uneventful Figure 21 B is a photograph made three years and two months after operation and shows some residual gynecomastia When last seen in December 1950 the breasts were continuing to regress He was otherwise normal

As stated previously there was little other than gynecomastia to suggest an adrenal tumor in this case The value for urinary 17 ketosteroids though slightly elevated for a boy of this age was not remarkable Furthermore calcification does not necessarily suggest an adrenal tumor Strong suspicion plus exploration established the cause

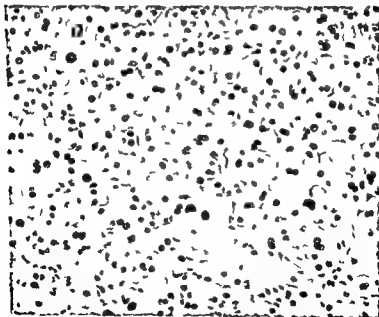


Figure 21 D Photomicrograph ( $\times 200$ ) of the benign cortical adenoma removed Patient alive and well eight years after operation (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital)



## In the Adult Male

**Incidence** In 1948 when Wilkins<sup>14</sup> reported the feminizing adrenal cortical tumor in the boy described above he also presented a review of feminizing adrenal tumors in males after puberty. To 1948 reports of 10 cases were found. Adding one previously unreported but studied by one of us (WWS) the total was brought to 11. Armstrong and Simpson<sup>3</sup> added another in 1948 after Wilkins report and in 1951 Mortensen and Murphy<sup>17</sup> added another the thirteenth. Recently three additional as yet unreported cases have been brought to our attention<sup>3, 10, 8</sup>.

**Diagnosis** In all cases reported to date gynecomastia has been present and a prominent feature. Depression or loss of libido was present in seven cases in the remaining six no information concerning libido is given. Atrophy of the testes is recorded in seven as is decrease or loss of sexual hair of male distribution. Obesity occurred in two but did not suggest Cushing's syndrome. In the majority a palpable abdominal tumor has been present and pyelograms have been of distinct value in localizing the tumor to the adrenal region.

Urinary hormonal studies have been made in six cases. In two urinary comb growth androgens have been normal and in these same two values for urinary estrogens determined biologically were high. In one additional case bioassay showed only a slight increase in urinary estrogen excretion.

Unfortunately total urinary 17 ketosteroids are reported in only four cases and the *beta* fraction in only one of these. In two elevation of the total is distinct in one less so and in the fourth values are normal. In the case studied by one of us total urinary 17 ketosteroids ranged from 196 to 213 mg per day preoperatively and over 95 per cent of this consisted of the *beta* fraction. Seventy

milligrams of dehydroisoandrosterone were isolated from one 24 hour specimen of urine

**Illustrative Case** The following case previously described in part by Wilkins<sup>11</sup> in his review and studied by one of us (W W S) while at the University of Chicago is presented in some detail as it illustrates certain prominent signs and symptoms common to the majority of cases of feminizing adrenal cortical tumors occurring in adult males

G B History No 349 103 The University of Chicago—University Clinics a man aged 42 years was admitted in 1945 to the Endocrine Service of Dr Allan Kenyon and subsequently transferred to the Urologic Service of Dr Charles Huggins Three months before he noted that his breasts had begun to enlarge and shortly thereafter that although his desire for intercourse was strong he was impotent On examination the breasts were enlarged and their areolae pigmented (Figure 22 A) a large mass was palpable in the right upper quadrant and flank and the spleen was enlarged Intravenous pyelograms revealed a large soft tissue mass displacing the right kidney downward (Figure 22 B) No definite pulmonary metastases could be seen on x ray Total 17 ketosteroids ranged from 196 to 213 mg per day preoperatively over 95 per cent of which consisted of the *beta* fraction A Friedman test for urinary gonadotropins was negative Through a transperitoneal incision a 1100 gram tumor was removed (Figure 22 C) which on section (Figure 22 D) proved to be an adenocarcinoma of the adrenal cortex with connective tissue being sarcomatous in nature During the first week postoperatively both adrenal cortical extract and DCA were used in the management The post operative course was complicated by symptoms and signs of thrombosis of the inferior vena cava Within one week of operation total urinary 17 ketosteroids had fallen to 14.5 mg per day (Figure 23) with reversion to a normal ratio of *alpha* and *beta* fractions Within five months a



Figure 22 A Feminization associated with an adrenal cortical carcinoma in a male age 42 years

chest x ray (Figure 24) revealed widespread pulmonary metastases and the following month the patient expired



Figure 22 II Intravenous pyelogram showing marked downward displacement and distortion of right kidney by a tumor mass

No urine specimen was obtained prior to the patient's death and hence urinary 17 ketosteroids could not be determined

**Treatment and Prognosis** Most cases of feminizing adrenal tumors have been far advanced when first seen



Figure 22 C The tumor in the gross (1100 grams)

and consequently prognosis has been poor. Only four of the 14 cases occurring in all age groups survived excision of the tumor and were free of metastases at the time they were reported. Two of these had not been followed sufficiently long to exclude recurrence.

At present surgical excision of the primary tumor prior to metastasis offers the only chance of cure. No data is available to permit evaluation of x-ray therapy either in conjunction with surgery or alone.

In view of the poor prognosis it would seem that for the present early and diligent search for the cause of any and all signs of feminization should offer men with tumor a better chance. Certainly this search should include determination of the urinary 17 ketosteroids.

### **Hormonally Active Medullary Tumors**

#### **Incidence**

Pheochromocytoma: Pick<sup>106</sup> in 1912 first suggested the term "pheochromocytoma" for tumors of the adrenal

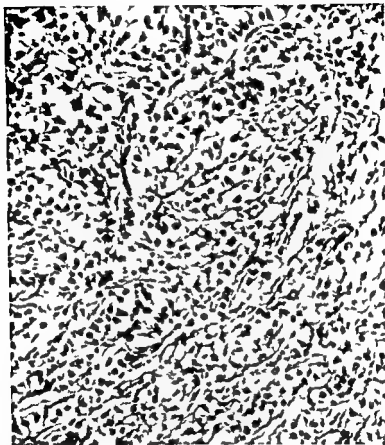


Figure 22 D Photomicrograph ( $\times 200$ ) of tumor showing "sarcomatous nature"

medulla reserving the term paraganglioma for chromaffin tumors in locations outside the adrenal and its immediate vicinity. Ten years later Labbe, Tinel and Doumer<sup>81</sup> reported the first case of paroxysmal hypertension due to a tumor of the adrenal medulla and in 1926 Vaquez and Donzelot<sup>12</sup> appear to have made the first diagnosis of a pheochromocytoma in the living subject. According to Howard and Barker<sup>6</sup> "The first report of

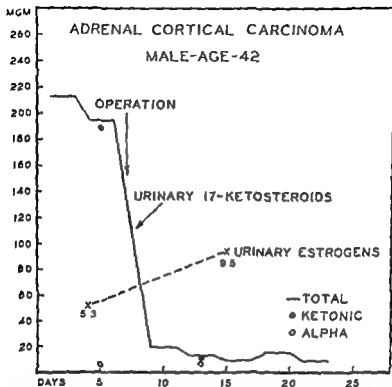


Figure 23 Urinary 17 ketosteroids and estrogens before and after removal of an adrenal cortical carcinoma associated with feminization in an adult male. 17 ketosteroids are expressed in milligrams per day; urinary estrogens in microgram equivalents of *alpha* estradiol benzoate per day. Note that prior to operation almost all of the total ketonic fraction was composed of *beta* 17 ketosteroids. Thereafter there was a reversion to a normal ratio of *alpha* and *beta* fractions. (Previously reproduced by Huggins and Bergenstal<sup>41</sup>)

an operative removal of such a tumor with relief of symptoms was made by C. H. Mayo.<sup>3</sup> The tumor was described in his article as a retroperitoneal malignant blastoma. After further cases with similar symptoms had been reported however the sections were reviewed and the diagnosis changed to pheochromocytoma.<sup>119</sup> Actually the first



Figure 24: Pulmonary metastases secondary to an adrenal cortical carcinoma associated with feminization in an adult male. (Refer to Figures 22 A, B, C and D)

report of a successful operation for this type of tumor that we have found was published by Roux<sup>117</sup> in February 1926. From the very brief description of the symptoms in his patient we feel quite sure that paroxysmal hypertension was present but no blood pressure determinations are given. The combination of correct preoperative diagnosis and successful surgical removal of a pheochromocytoma



cytoma with paroxysmal hypertension was first relieved by Pincus<sup>101</sup> and Shipley<sup>112</sup>

Although a pheochromocytoma is a comparatively rare tumor over 200 cases have been reported to date. Having been observed with equal frequency in the male and female it occurs usually between the ages of 20 and 50 years though the extremes of seven and 71 are reported. According to Brines and Jennings<sup>16</sup> almost 90 per cent of these tumors are in the adrenal with a slight but definite predilection for the right side. In Cahill's<sup>1</sup> series of 15 cases involving 17 tumors seven were located outside the adrenal one of which was in the neck. Phillips<sup>101</sup> has reported an occurrence of this tumor in the thorax.

Calkins and Howard<sup>2</sup> were able to find 15 patients with bilateral tumors five of which were malignant. In this report they present two most interesting cases of bilateral tumors studied by them and operated by Colston occurring in blood relations aunt and niece. Of further interest was the history that the latter's mother and former's sister had died at age 28 of paroxysmal hypertension. The niece has died of metastases since this report. Sprague *et al*<sup>116</sup> estimate that these tumors are bilateral in at least 10 per cent of cases and that they may be malignant in perhaps 10 per cent. Karsner<sup>77</sup> estimates malignancy as being of the order of 8 per cent. Ten cases have been reported as occurring in the organs of Zuckerkindl—those small nests of paraganglion cells associated with the sympathetic plexuses and located along the aorta near the root of the inferior mesenteric artery (Warborough<sup>155</sup>).

## Diagnosis

**Symptomatology.** There appears to be little question but what the symptoms associated with pheochromocytomas are secondary to release into the blood stream of

epinephrine or norepinephrine. However from a review of the symptoms in proved cases it appears likely that no constant pattern is observed but rather several patterns seemingly dependent on which vasopressor substance is released in what quantities and whether intermittently or continuously. Thus tumors have been found in the following types of cases: (1) those in which no symptoms have been elicited and in whom a tumor is found at autopsy; (2) those in which there are characteristic reproducible paroxysms of hypertension and associated symptoms; and (3) those in whom the chief symptom or finding is sustained hypertension simulating either the essential or malignant type.

Cases of true pheochromocytoma without cardiovascular symptoms or signs are distinctly in the minority, probably representing less than 10 per cent of all. In a recent report of five cases of pheochromocytomas unsuspected prior to autopsy, Berkeiser and Rappoport<sup>1</sup> review the histories in some detail. Mild to moderate hypertension was present in four of the five, only one presenting no signs or symptoms of a cardiovascular nature. At autopsy two days after a combined abdominoperineal resection for a carcinoma of the rectum a 4 cm pheochromocytoma of the left adrenal was found. In addition multiple neurofibromas were present as well as liver metastases histologically like the primary rectal tumor.

Characteristically pheochromocytomas give rise to paroxysms of hypertension accompanied by anxiety, headache, precordial and epigastric distress, palpitation, sweating, pallor, coldness of the extremities and nausea or vomiting. Roughly one third to one half of patients with these tumors have attacks of this general pattern, varying somewhat from patient to patient and in degree. However this varies for in a series of 25 patients studied by Sprague, Kvale and Priestley,<sup>1\*</sup> the tumors of 14 were

considered to be functioning paroxysmally. According to Wells and Bowman<sup>143</sup> the incidence of chronic hypertension in patients with functioning tumors increases with time. This appears logical as commonly it has been observed that as the disease progresses the interval between attacks becomes shorter and shorter.

Paroxysmal attacks secondary to pheochromocytoma must be differentiated from every anxiety attacks. This may be difficult. In a review of 12 cases seen at The Johns Hopkins Hospital Howard<sup>61</sup> was impressed that whereas at times a paroxysm appeared to be precipitated by anxiety or exertion more frequently manipulations causing pressure on the tumor or metabolic changes such as hypoglycemia appeared responsible. Furthermore most patients with tumors were emotionally stable. At times an indescribable aura preceded a paroxysm and always precordial pain followed rather than preceded the hypertension. Smithwick *et al*<sup>144</sup> have been impressed with the frequency with which all patients with tumors whether associated with persistent or paroxysmal hypertension manifest other pharmacological effects of epinephrine release. Howard's experience is similar in that over half of his patients perspired almost continuously several had rapid pulse and a low grade fever and one third had basal metabolic rates greater than +15. Although diabetes occurred in two patients with pheochromocytomas and was relieved by removal of the tumor he was not impressed with the frequency of association of the two conditions believing that hypertension and diabetes were more apt to occur as a coincidence.

As noted above the majority of patients with pheochromocytomas do not have paroxysms but present themselves with clinical pictures indistinguishable from that of essential or malignant hypertension. As a consequence pharmacological means have to be used to differentiate

these diseases. In Smithwick's<sup>15</sup> series of 1 000 cases of hypertension subjected to lumbodorsal sympathectomy exploration of both adrenals at the time revealed five pheochromocytomas (0.5 per cent).

**Pharmacologic Tests** In general these are of two types: (1) those designed to stimulate/discharge of pressor compounds from the tumor and (2) those designed to lower/blood pressure by competitive inhibition of the pressor compounds released by the tumor. In general these aids have been of great/help.

The histamine test introduced by Roth and Lurie<sup>116</sup> in 1945 belongs to the first group—those agents which stimulate discharge of pressor compounds from the tumor—and hence mimic a paroxysmal attack. It has been the experience of many that this test has been most useful in establishing the cause of paroxysmal hypertension whereas in patients with sustained hypertension competitive drugs such as benzodioxan etc. are preferred.

It should be emphasized from the start that a *negative histamine test does not rule out the presence of a pheochromocytoma*. Care in conducting the test reduces the number of false negatives to a very few. Of consequence it becomes important to heed the recent admonitions of Dr. Grace Roth<sup>117</sup> who has had the most experience with this test. Prior to the test the patient should not have had any sedation for a minimum period of 12 hours. He should not have had any thiocyanate for four to six days or until thiocyanate can no longer be detected in the blood and a cold/pressor test should be performed.

Important in conducting the test itself are the size of the dose, the way the drug is administered and the frequency of determination of the blood pressure after administration of the drug. Roth stresses that small doses of histamine increase the margin of safety and suffice to stimulate an attack. Thus she recommends a dosage of

0.01 to 0.05 mg histamine base intravenously, but never more. It is best administered through one of the ports of a three way stopcock while a slow intravenous infusion of saline is running to avoid the possible effect of venipuncture on the blood pressure.

After giving the drug intravenously to a patient with a pheochromocytoma and if blood pressure determinations are made with sufficient rapidity within 30 seconds there is a fall in blood pressure. Immediately thereafter the blood pressure rises and reaches a peak within one to three minutes. This rise exceeds by some 100 mm the elevation initially obtained by the cold pressor test. Such is not the case in normal individuals hyperreactors to the cold pressor test nor those with established hypertension. Often in hypertensives with a labile blood pressure the elevation in blood pressure may be greater in four to ten minutes after injection than at two minutes. Figure 25 illustrates a typical positive histamine test in a patient with paroxysmal hypertension in whom a pheochromocytoma was removed by one of us (WWS). Her blood pressure response to cold is shown for comparison. (This woman's case history is described in detail elsewhere by Dr. Robert E. Mason<sup>8</sup> being one of two in which negative benzodioxan tests were observed but in both of which histamine tests were positive.)

Some internists have criticized the histamine test not only on the basis of the several false negative reactions observed but because of violent hyperreaction with the possibility of a cerebral accident, pulmonary edema or an ocular hemorrhage. It is the feeling of Howard<sup>11</sup> and the authors that in the presence of persistent hypertension with obvious vascular damage the histamine test is best omitted but in patients with paroxysmal hypertension who are normotensive between attacks the test gives much reliable information and no more danger will result

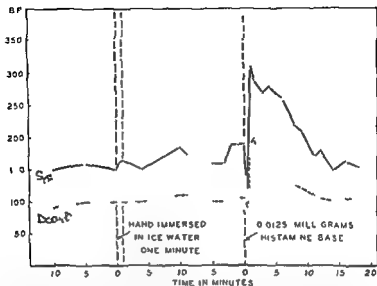


Figure 25 Cold pressor and histamine tests prior to removal of a pheochromocytoma. Tests were done in succession on the same day. Note that maximum systolic pressure after histamine exceeds that following cold by more than 100 mm mercury.

from a histamine induced paroxysm than one occurring spontaneously.

Other agents belonging to the group which stimulate an attack include etamon® (tetraethylammonium) and mechoyl®. Neither has proved as satisfactory as histamine.

As stated above in the determination of the cause of persistent hypertension drugs which act as competitive inhibitors of the pressor compounds released by the tumor are to be preferred. Three examples of such drugs are benzdioxan, dibenamine hydrochloride and regitine®.

In 1947 Goldenberg, Snyder and Aronow<sup>43</sup> introduced the use of 2-(1-piperidylmethyl)-1,4-benzodioxan (piperoxin 933, Fourneau or benodaine®) in the diagnosis of

0.01 to 0.05 mg histamine base intravenously, but never more. It is best administered through one of the ports of a three way stopcock while a slow intravenous infusion of saline is running to avoid the possible effect of venipuncture on the blood pressure.

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longer. Three to five days are required for full recovery from a single injection during which time it is impossible to counteract its action with epinephrine. Its recommended test dose is 7 mg. for each kilogram of body weight dissolved in 300 cc. of 5 per cent dextrose and given intravenously over the course of one hour. Because of the frequency of untoward/side reactions and false positive tests in patients with essential hypertension few recommend its use for the differential diagnosis of pheochromocytomas.

In 1951 Grimson and his associates<sup>2</sup> reported their experiences with regitine® (2 (N p tolyl N (m hydroxy-phenyl) aminomethyl) imidazoline hydrochloride) as a routine testing agent for pheochromocytoma in patients with hypertension. A single intramuscular injection of 5 mg. serving as the test dose. In patients with proved tumors regitine® produced a reduction of blood pressure which lasted longer than that produced by benzodioxan and in addition was associated with fewer/side effects and with less fluctuation in blood pressure in patients with hypertensive vascular disease. As noted above it appeared to offer no advantage over benzodioxan in overcoming the false/positive tests so frequently observed in uremia although no false/negative tests have been encountered to date. As yet we have had no experience with the drug.

**Röntgenologic Aids.** Numerous radiologic techniques have been introduced to aid in preoperative localization of the tumor once the diagnosis has been established by symptomatology and pharmacologic tests. These have included perirenal insufflation with air or oxygen laminography and aortography. Whereas it is always gratifying to have a nice preoperative film demonstrating a tumor it has always seemed to us that this is of little importance



pheochromocytomas associated with persistent hypertension. This drug appears to be a true competitor of epinephrine and norepinephrine although some question competitive action with the latter.

This test is carried out in a similar fashion to that described for histamine. However according to Howard barbiturates do not interfere with the test. Following intravenous administration of the currently recommended test dose of piperoxan over a two minute period (15 mg total or 0.25 mg for each kilogram of body weight), the blood pressure is carefully recorded and the overall response of the patient noted. A positive response indicating the probable presence of a pheochromocytoma consists in a significant drop in both systolic and diastolic blood pressures starting within two to three minutes after injection and returning to control levels within 20 minutes. *Not all patients with persistent hypertension due to a proved pheochromocytoma give positive tests.* In the series studied by Goldenberg and his associates.<sup>4</sup> Fifty-nine patients with operatively demonstrated pheochromocytomas have shown positive benzodioxan tests while only three false negative tests have been observed. Others including Calkins, Dini and Howard,<sup>104</sup> Placc,<sup>105</sup> and Meilman<sup>106</sup> have observed false negative tests.

False positive tests may also occur. Grimson and his associates<sup>107</sup> in a recent paper which dealt with the comparative merits of benzodioxan and regimine<sup>9</sup> found that both drugs gave false positive values in 5 of 11 patients with hypertensive vascular disease and uremia.

Dibenzamine hydrochloride (N-dibenzyl-beta-chloroethylamine hydrochloride) has also been used successfully as a test for pheochromocytoma in patients with persistent hypertension. Like benzodioxan it appears to be an epinephrine competitor but one which acts much



Figure 26 Percutaneous aortogram demonstrating pheochromocytoma of right adrenal (method of Peirce<sup>101</sup>) (Courtesy of Dr Elmer Belt and Dr Willard H Goodman University of California at Los Angeles )

particularly in view of our belief that transperitoneal exploration of both adrenals and periaortic ganglia should be carried out in every case in which pheochromocytoma is suspected. In three recent cases of pheochromocytomas seen at The Johns Hopkins Hospital the tumors were correctly localized with laminograms. This technic however could not be expected to reveal small extra adrenal tumors.

Although we have made a number of aortograms for other purposes we have not used this technic in cases of suspected pheochromocytoma. Recently we were unable to demonstrate a 4 cm. adrenal cortical tumor by percutaneous aortography. Most recently however my former associate Dr. Willard E. Goodwin now in charge of Urology at the University of California at Los Angeles sent me serial aortograms which he and Dr. Elmer Belt had made preoperatively according to the percutaneous method of Pearce<sup>124</sup> in a boy with a pheochromocytoma which at operation replaced the right adrenal. Through their courtesy one of the postinjection films showing excellent localization of the tumor is reproduced in Figure 26. No untoward side effects were noted in this patient nor have we experienced any in our rather large series done for other purposes.

**Examination of the Urine.** In a recent communication A. Engel and U. S. von Euler<sup>125</sup> report greatly increased urinary excretion of norepinephrine epinephrine in two cases of proved pheochromocytoma in which these determinations were made. Of further interest was the observation that the proportions of both pressor substances were approximately the same as in the tumors removed. After the removal of the tumors the norepinephrine epinephrine output in the urine fell quickly to normal in both cases. It is hoped that this highly exciting work will be extended.

equivocal a histamine test reproduced in all details one of the spontaneous attacks described with the blood pressure rising to over 300 mm systolic over 190 diastolic after a transient fall. This rise exceeded by much more than 100 mm the elevation obtained by a cold pressor test. An intravenous pyelogram was unsatisfactory but a lymphogram suggested a small mass above the left kidney. A diagnosis of a pheochromocytoma causing paroxysmal and sustained hypertension was made and shortly thereafter one of us (WWS) carried out exploration of the adrenals through an upper transverse abdominal incision. The right adrenal was normal; the left adrenal was involved in tumor. This tumor measured 4 centimeters in diameter, was reddish brown in color and seemed to be fused with a normal appearing gland which necessitated partial adrenalectomy to insure removal of all of the tumor. After removal of the tumor and for the next 24 hours her blood pressure was maintained with dilute epinephrine solution (1 milligram per 100 cubic centimeters of fluid) at 120/80 to 140/100 regulating the rate of flow according to the blood pressure. In all during this period she received 22 milligrams. Convalescence thereafter was essentially uneventful. Histamine and benzodioxan tests done on the tenth postoperative day gave normal pressure responses. She was discharged on the following day and has remained well to date.

### **Medullary Tumors with No Recognizable Hormonal Activity**

#### **Neuroblastoma (Sympathicogonoma and Sympathicoblastoma)**

**Incidence** Whereas incidence figures are to be found in the literature for neuroblastomas, no data can be found giving the incidence of sympathicogonomas and sympathicoblastomas individually. Generally the suffix blastoma is used to indicate a more malignant tumor but

**Illustrative Case**

E G History No 527036 The Johns Hopkins Hospital  
a housewife aged 28 years was admitted in 1950 to the  
Medical Service of Dr E C Andrus with the complaints  
of high blood pressure and albumin in the urine She re-  
called that at age 14 her blood pressure was 140 and on  
admission to college was 160/100 remaining at that level  
until 1949 In the spring of 1947 she began to experience  
rather frequent severe headaches which were associated  
with profuse perspiration These headaches would come  
on at any time of day would last about an hour and  
spontaneously go away She became pregnant late in 1948  
or early 1949 and in September 1949 delivered spon-  
taneously a full term living male child Several blood  
pressure readings ranged close to 180/110 and 2 plus  
albumin was found on repeated urine examinations On  
discharge eight days postpartum her blood pressure was  
145/110 Inquiry revealed that in the third trimester  
of her pregnancy the character of her headaches had  
changed These would begin with a sense of nausea in  
the pit of her stomach and a feeling of malaise with mild  
joint aches Shortly thereafter she would experience  
severe aching pain in the occipital part of her head with  
radiation to both frontal areas These were described as  
steady and crushing in character and were associated with  
pounding of her heart as if it were too large for my  
chest Her face would blanch and she would perspire  
profusely These attacks appeared to come on more fre-  
quently when she was hungry would last for about an  
hour and when gone would leave her feeling fine Daily  
blood pressure examinations after admission to The Johns  
Hopkins Hospital showed wide fluctuations ranging from  
over 300 to as low as 140/90 She was observed to suffer  
attacks similar to those described in the history with  
nausea followed immediately by flushing and palpitation  
aching of the joints dyspnea sweating and blood pressure  
elevation to over 300 Whereas a benzodioxan test was

tal system. As a result symptoms vary from case to case. As in Wilms tumor frequently no symptoms occur and the infant is brought to the physician because the mother has felt an abdominal mass. As the tumor grows and metastasizes multiple symptoms occur which depend upon involvement of nearby structures, the site of distant metastasis and the ability of the child to express his feelings. Frequently the infant shows evidence of wasting. Diarrhea or constipation, jaundice, anemia and generalized toxemia are usually secondary to extensive liver involvement.

In the three cases from which we have drawn illustrative material (Figures 27 through 33) in the first attention was directed to the tumor by the mother feeling an abdominal mass, in the second the physician palpating the tumor while examining the infant for upper respiratory infection and in the third when the parents sought medical attention for their 4½ year old



Figure 27 Postoperative appearance of a 17 month old girl following surgical excision of a sympathicogonioma. Excision preceded by x-ray therapy resulting in an estimated 50 per cent decrease in the size of the tumor mass. Outcome fatal.

Karsner<sup>73</sup> uses the term to indicate a higher degree of differentiation than is true of the sympathicogonioma. Furthermore, he states: "Practically, the sympathicoblastoma is less malignant than the sympathicogonioma especially when it occurs in later periods of life."

Occurring with equal frequency in either sex and in or near either adrenal, these tumors are found almost entirely in young children, some 80 per cent within the first five years of life. Those occurring in the older group are usually less malignant and most often are sympathicoblastomas. Neuroblastomas are the most common sympathetic tumors in childhood and to date approximately 400 cases have been reported, an incidence quite like that of Wilms' tumor of the kidney. Whereas they usually are unilateral, bilateral tumors have been observed.

Until recently distinction was made between Pepper and Hutchison types, the former referring to neuroblastomas of the right adrenal principally metastatic to the liver, the latter including tumors of similar histology arising in the left adrenal principally metastatic to the skull. However, analysis of cases by Farber,<sup>74</sup> Karsner,<sup>75</sup> and others<sup>130</sup> has shown that the distribution of the metastases is not determined by the histologic character or the anatomic site of the original tumor. Hence these eponymic designations are not justified. Wittenborg<sup>131</sup> studying 73 cases of neuroblastoma observed that the upper abdomen was the primary site of the tumor in 74 per cent, some 60 per cent had metastasized at the time of diagnosis.

## Diagnosis

**Symptoms.** Usually attention is directed to a neuroblastoma by the presence of a painless, nontender abdominal mass or because of metastases to the liver or skeletal

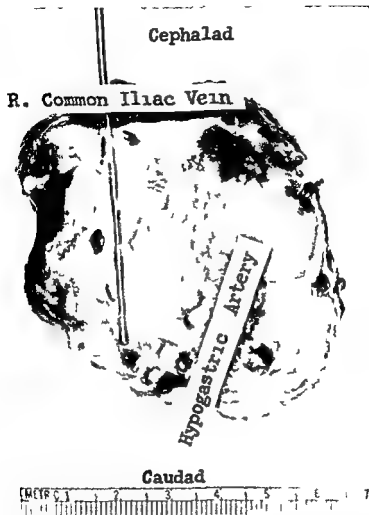


Figure 29 A A gross appearance of a sympathecogonioma which in order to be removed required resection of portions of the right hypogastric artery and right common iliac vein B photomicrograph ( $\times 200$ ) of the tumor showing rosette formation characteristic of sympathecogoniomas (Courtesy of Dr Richard Kieffer and Dr Glenn Morrow The Johns Hopkins Hospital)





U 1664-48

Figure 26 Gross appearance of sympathetomoma (Refer to Figure 27)

son shortly after he had complained of abdominal pain and they had noticed a lump on his head which had increased in size and was associated with a "blood shot eye as if a blood vessel had burst"

**Signs** The presence of an abdominal mass on physical

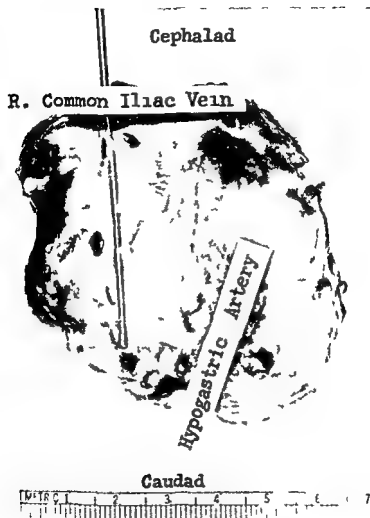


Figure 29 A. A gross appearance of a sympathicogonoma which in order to be removed required resection of portions of the right hypogastric artery and right common iliac vein. B photomicrograph (x200) of this tumor showing rosette formation characteristic of sympathicogonomas. (Courtesy of Dr Richard Kieffer and Dr Glenn Morrow, The Johns Hopkins Hospital.)

examination of an infant or young child immediately suggests a neuroblastoma or a Wilms tumor of the kidney. Skeletal x rays and excretory urograms often establish the diagnosis. Whereas skeletal metastases are quite common in neuroblastoma they are rare in Wilms tumors. Although a neuroblastoma may invade the kidney and present a pyelogram which suggests a renal embryoma

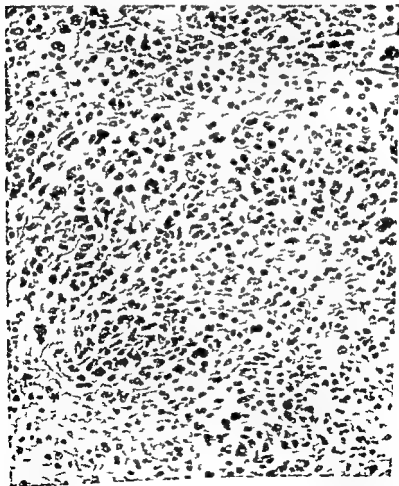


Figure 29 II



Figure 30 A A preoperative intravenous pyelogram in a patient with a pelvic sympathicogonoma (Refer to Figures 29 A and B ) Note pronounced lateral displacement of both ureters right by droureteronephrosis and left hydroureter B intravenous pyelogram in same patient six months after removal of tumor The course of both ureters is straight and only slight ectectasis and pvelectasis persist on the right

this is unusual. Most frequently neuroblastomas appear as extrarenal masses displacing the kidney downward when arising in the adrenal or causing lateral displacement of the ureters when arising lower in the abdomen with pvelographic signs of back pressure when large enough to obstruct (Figure 30 A). At times both neuro



Figure 30 B

blastomas and renal embryomas are calcified (Figure 32)

Neuroblastomas are distinguished from hormonally active tumors by the absence of symptoms and signs suggestive of adrenal cortical or medullary secretion as outlined previously. Wilkins<sup>146</sup> however has observed a 7<sup>14</sup> year old girl with a tumor which resembled a neuroblastoma who clinically had severe hypertension and whose benzodioxan test was positive. Upon staining the fresh tumor tissue with ferric chloride the chromaffin reaction was not seen and on assay only a minute amount of epinephrine was obtained.

Diagnosis is established by biopsy either aspiration or surgical of the tumor or a metastasis.

### Treatment

It appears that physicians associated with The Children's Medical Center in Boston have had the greatest experience in the treatment of neuroblastomas and the inter-



Figure 31 Pathetic appearance of a boy age one and one half years secondary to disseminated neuroblastoma. Biopsy of scalp lesion was positive for neuroblastoma. Transient improvement followed each course of nitrogen mustard but death occurred three weeks after last course. (Courtesy of the Department of Pediatrics, The Johns Hopkins Hospital.)

this is unusual. Most frequently neuroblastomas appear as extrarenal masses displacing the kidney downward when arising in the adrenal or causing lateral displacement of the ureters when arising lower in the abdomen with pyelographic signs of back pressure when large enough to obstruct (Figure 30 A). At times both neuro



FIGURE 30 B







Figure 32 Calcified mass in right upper quadrant representing the primary tumor in a patient with a disseminated neuroblastoma" (Refer to Figure 31 )

ested reader is referred to the original papers of Farber<sup>23</sup> Wyatt and Farber<sup>14</sup> and Wittenborg<sup>19</sup> of that institution for details. The latest communication by Wittenborg (1950) reviews in detail 73 cases subjected to no specific treatment: surgery alone or surgery and postoperative roentgen therapy, and to this we wish to refer.

In the group of 28 cases in which no specific therapy was carried out, 20 had metastases when first seen, all died within one year. The remaining eight when first seen appeared to have localized tumors. Of these three died within 12 months of local or distant spread, one died with metastases 10 years after the diagnosis, two were discovered incidentally at autopsy and two are alive and well 12 and 16 years after diagnostic biopsy.

In 12, therapy consisted of surgical excision of the primary tumor only. Seven (58 per cent) survived three years or more. Six of seven in whom the primary tumor appeared to be localized to the abdomen survived three years or more, a survival rate of 85 per cent for this particular group.

Eleven patients received x-ray therapy after surgery but not before. Two with skeletal metastases at the time postoperative therapy was begun died within 18 months. Nine tumors appeared to be localized after preoperative study and at surgery. In three of these the surgeon felt that excision was complete; in six tumor tissue was known to have been cut across and put left behind. Four in the latter group (60 per cent) are living and well, having been followed three to nine years.

Twenty-two patients underwent biopsy only, followed by x-ray therapy. One died within one week after treatment was begun. Six of the remaining 21 patients with metastases are living and well three to 12½ years after x-ray therapy (27 per cent). The remaining 15 patients

with metastases all died within the year after biopsy and initiation of x ray therapy

Wittenborg concludes that early detection and complete surgical excision of the apparent local tumor offers the best prognosis. However if no distant metastases can be demonstrated and surgical excision is incomplete x ray therapy still offers a good prognosis. Furthermore "primary neuroblastoma in the abdomen with metastases to the liver however still offers an excellent prognosis if treated by irradiation. A 100 per cent three year survival in this group of six patients is reported

For a detailed discussion of the technic of roentgen therapy in these cases the radiotherapist should consult Wittenborg's original article. Of particular interest to one who is not a radiologist were Wittenborg's observations supporting immediate postoperative therapy without waiting for complete healing of the incision. No wounds broke down.

At this writing no reports are available to aid in assessing the value of radioactive drugs nitrogen mustard or anti folic acid compounds in the treatment of disseminated neuroblastoma. However Wittenborg<sup>10</sup> calls attention to a forthcoming report of 21 patients so treated by Dr Sidney Farber and associates Department of Pathology The Children's Medical Center Boston.

In concluding this discussion of neuroblastomas the following case is presented which illustrates many of the features involved in diagnosis and treatment.

R.D. History No. A 94846 Hurriet Lane Home for Invalid Children of The Johns Hopkins Hospital a boy aged one year and three months was apparently well until three months prior to entry here. The child was taken to the family physician because of a cold and on physical examination a large mid abdominal mass was

felt. Intravenous pyelograms revealed that this mass had caused marked lateral displacement of both ureters, right hydroureteronephrosis and left hydroureter (Figure 30 A). At exploratory laparotomy elsewhere the tumor was judged to be inoperable. A biopsy revealed a "neuroblastoma." The patient was referred here for x-ray treatment. Following two courses of nitrogen mustard therapy judged to be ineffective the patient was again explored (Drs. R. Kieffer and G. Morrow) and by resecting portions of the right hypogastric artery and right common iliac vein it was possible to remove the tumor apparently intact. Figure 29 A shows the operative specimen and Figure 29 B a section from it. Postoperative convalescence was quite uneventful and within two weeks x-ray therapy was begun. The pretreatment factors were 250 kVp, 15 mAs, 5 cu. in. of 50 STD, 17 hvi calculated to deliver 3000 r D. During a period of approximately two months the child received 49 treatments equally divided between two ports. This resulted in a final tumor dose of 2600 r to the midline of the abdomen. Because the hematopoietic system would not tolerate higher daily doses than 50 to 75 r per day per one field, a shorter course with larger daily doses as suggested by Wittenborg<sup>12</sup> was out of the question.

At this writing, over six months since operation the child is living and well. Intravenous pyelograms reveal good kidney function, right and left, with only slight ectasia and pyelectasis (Figure 30 B). The course of both ureters is straight. Bone and chest films reveal no metastases.

**Ganglioneuroma.** As stated at the beginning of this chapter Stout<sup>13</sup> divides ganglioneuromas into two groups: (1) those that are well differentiated and usually benign and (2) those that are incompletely differentiated and rather often malignant.

### **Benign Ganglioneuroma**

**Incidence** McFarland and Sappington<sup>24</sup> in a review of the literature in 1935 found records of 143 cases. Occurring more commonly in females than males over one half have been reported in patients under 20 years of age. However they may occur at any age. Frequently they are an incidental autopsy finding. Located most frequently in the posterior mediastinum they also occur in the paravertebral sympathetic ganglia and in the adrenal medulla. Over 80 per cent of all ganglioneuromas are benign.

**Gross and Microscopic Appearance** : Benign ganglioneuromas are round to oval in shape, grayish white on cross section, fairly well encapsulated and although at times they reach huge dimensions do not invade locally or metastasize. Derived from mature sympathetic nerve cells, these tumors are composed of mature ganglion cells intermixed with countless nerve fibrils which are twisted and irregular in appearance and without connection with an end organ (Figure 33). Characteristically the ganglion cells are large, round to oval in shape and contain one or two round nuclei with prominent nucleoli. Cytoplasmic processes may be prominent and at times the nerve sheaths may show microcystic changes.

**Symptoms** Benign ganglioneuromas are usually silent but may give rise to signs and symptoms as a result of their interference with local functions by means of the pressure caused by the expanding growth.

**Treatment** Surgical excision if necessary.

### **Malignant Ganglioneuroma**

Stout<sup>25</sup> reports that about one-fourth of all ganglioneuromas are incompletely differentiated. These he divided into two groups. "In one the ganglion cells of the

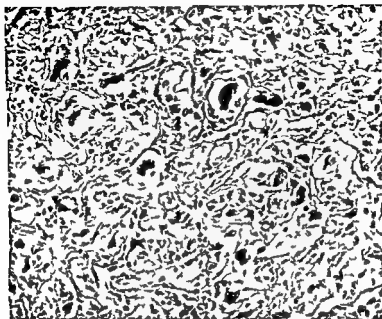


Figure 33 Photomicrograph ( $\times 200$ ) of a benign ganglioneuroma in this instance an incidental autopsy finding (See text for description of histology)

entire tumor show a mixture of cells varying from undifferentiated sympathicoblasts up to fully or incompletely differentiated ganglioneuroma while another contiguous portion will be a characteristic sympathicoblastoma. Of this type 65 per cent produce metastases."

Removal of the tumor is the treatment provided there is no clinical evidence of metastases. Karsner<sup>3</sup> states "There is no proof that irradiation is curative

## VI

### SURGICAL TREATMENT OF ADRENAL TUMORS

(*Excluding Cushing's Syndrome*)

#### SURGICAL ROUTES

SINCE GORDON HOLMES<sup>7</sup> first successfully removed an adrenal cortical tumor in 1924 and Charles Mayo in 1927<sup>83</sup> removed what proved to be a pheochromocytoma numerous surgical approaches to the adrenal have been proposed. These include every conceivable route.

Thus Crile<sup>8</sup> (1932) denervating the adrenals "made the approach along the lumbar back muscles through a vertical incision. Later he used a modified kidney incision. This modified kidney incision ran from behind forward immediately beneath and to the midportion of the twelfth rib where it turned and was carried vertically downward. Koster *et al*<sup>9</sup> (1931) advocated an incision extending from the tip of the twelfth rib obliquely to the anterior superior spine down through the muscle wall and fascia to the perirenal fat. Prior to adrenal exploration they opened the peritoneal cavity and explored the pelvis. Broster and Vines<sup>1</sup> (1933) in performing unilateral adrenalectomy for female pseudohermaphroditism with congenital adrenal hyperplasia employed the trans-thoracic approach. Walters<sup>141</sup> (1934) in dealing with tumors used a lateral posterior lumbar incision—similar to that used in approaching the kidney. Calhoun<sup>19</sup> (1936) operating for adrenal cortical tumors recommended an "oblique incision (beginning) at the ensiform and ex-

tended along the costal flare until adequate exposure was obtained—exposure (was) facilitated by use of an elevated bridge on the table situated so that the costal flare is opened and the subcostal area projected forward" Young<sup>14</sup> (1936) advocated simultaneous exposure of the adrenals through posterior verticollateral incisions and devised a special self retaining retractor to aid in the procedure Zintel *et al*<sup>15</sup> (1951) in performing subtotal ("95 per cent") adrenalectomy for hypertension recommend exposure of the adrenal "through a lateral subcostal incision with the patient in the lateral decubitus position and the kidney rest or kidney bar of the operating table three inches cephalad to the lowest point of the costal margin" They found it unnecessary to resect the twelfth rib Huggins and Bergenstal<sup>16</sup> (1951) performing bilateral adrenalectomy in patients with disseminated cancer who relapsed some time after orchiectomy and estrogen therapy "find that the posterolateral approach gives incomparably the best exposure—An incision 20 to 25 cm long is made in the loin over the 12th rib which is resected the fascia of Gerota is incised" Earlier Huggins and Scott<sup>17</sup> (1945) used a similar incision without rib resection Crimson<sup>18</sup> (1951) has most recently advocated a transthoracic and transdiaphragmatic approach which "permits palpation of the abdominal content through an incision in the left diaphragm"

That the exposure and removal of a localized adrenal tumor at times is difficult is not denied no matter what the surgical approach In our experience no one approach is suitable for dealing with all types of adrenal pathology Though some will disagree the following suggestions based on our experience are offered

### Pheochromocytoma

Once the diagnosis of a pheochromocytoma has been made on clinical grounds it is established on finding a



tumor at exploration. Treatment is clearly surgical removal of the tumor. Two important considerations are 1) which approach to use and 2) how to manage the patient during and after operation.

Because it has been amply demonstrated that pheochromocytomas may arise in both adrenals outside the adrenal in its immediate vicinity and along the aorta and sympathetic chain all these regions must be explored. We believe that this is best accomplished through a transverse upper abdominal incision which transects both recti. The procedure is best carried out under general anesthesia using ether administered through an endotracheal tube.

Customarily we expose the left adrenal first mobilizing the spleen medially and the kidney inferiorly. Four broad Deaver retractors whose blades are protected with Mikulicz pads serve admirably in exposing the posterior peritoneum above the kidney and anterior to the adrenal. After incising the peritoneum the tumor or adrenal which may have been palpable on approaching this area usually presents itself. The blood supply cannot be defined for tumor as it can for the majority of normal adrenals. Preliminary to removal of a tumor whether it is a part of or distinct from the left adrenal the right adrenal area is explored retracting the liver upward the intestines medially the kidney downward and the lateral belly wall outward again with four broad Deaver retractors.

If only one tumor is found and it is in such close association with one adrenal as to make it impossible or unwise to remove only the tumor both the tumor and the adrenal are removed provided the opposite adrenal is grossly normal. If both adrenals are involved partial resection of the adherent normal gland may have to be done although in such cases the risks of recurrence of tumor and adrenal insufficiency are great.

Subsequent to exploration of both adrenal areas the

entire abdomen should be explored generally beginning in the region of the paraortic sympathetic ganglionic chain. Furthermore it is important to recall that tumors have been reported to have occurred in the thorax and neck. Consequently it is wise to check all patients post-operatively with pharmacologic tests to determine if all tumors have been removed.

### Adrenal Cortical Tumors

Whereas we agree with Priestley *et al*<sup>111</sup> that if Cushing's syndrome is secondary to an adrenal cortical tumor the contralateral gland frequently appears atrophic we have never observed atrophy of the adrenal on the side opposite to a cortical tumor which had resulted in virilization or feminization. Consequently in the latter group we see little need of exploring both sides if the tumor has been localized preoperatively. The selection of the surgical route will depend largely on which approach we feel will give us best exposure whether it is transthoracic, transperitoneal or lumbar. We have used them all. A good illustration of how one must modify the approach to suit the particular case is that of a 4½ year old boy with uncomplicated adrenogenital syndrome treated in The Johns Hopkins Hospital in 1948 and again in 1949 the details of which are published<sup>112</sup>. Preoperative pyelograms demonstrated a very large calcified mass in the region of the right lobe of the liver which had caused little if any distortion of the right kidney (Figure 34). Transperitoneal exploration of this mass by one of us (W W M) revealed that it was entirely embedded in the right lobe of the liver and that if the tumor were to be removed in its entirety one would have to resect the major share of this portion of the liver. The operation was terminated without attempting this. However one year later Dr Ravitch and one of us operated again through a transverse right



Figure 34 Plain film of abdomen showing calcified area in right lobe of liver in a young boy with uncomplicated adrenogenital syndrome. At operation this proved to be a calcified adrenal cortical adenoma embedded in the right lobe of the liver the major portion of which had to be excised in order to remove the tumor. Patient alive and well three years later.

upper quadrant incision so modified however as to permit excision of several costal cartilages. This exposure permitted excision of the major portion of the right lobe of the liver and the entire tumor (Figure 35). Admittedly this would have been very difficult or impossible through any other type of incision.

### HORMONAL MANAGEMENT AT OPERATION

We agree wholeheartedly with Kepler and Locke<sup>8</sup> that the management of cases of functioning adrenal tumors is best accomplished by close cooperation between the surgeon and the internist. Prior to operation all fore

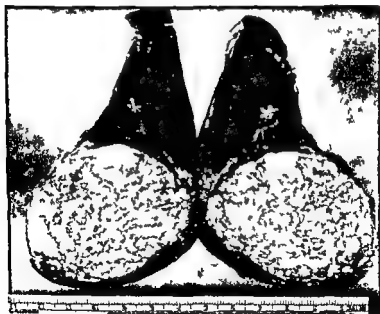


Figure 35 Major portion of right lobe of liver containing an encapsulated calcified adrenal cortical adenoma which was associated with the adrenogenital syndrome in a young boy<sup>147</sup> (Refer to Figure 34)

seeable problems in management are discussed plans agreed upon and preparations made to carry out these plans

### **Pheochromocytoma**

Some difference of opinion exists as to what constitutes optimum hormonal therapy in conjunction with the removal of a pheochromocytoma. This revolves around considerations of medullary function few advocating cortical replacement therapy.

It has been the experience at The Johns Hopkins Hospital<sup>41</sup> that frequently following removal of a pheochromocytoma the blood pressure falls precipitously and the patient is in a state of shock. In recent years this has been successfully combatted in every instance by a continuous intravenous infusion of 5 per cent glucose containing 15 mg of epinephrine per 100 cc regulating the rate of flow according to the level of the blood pressure. Nothing has been done to counteract the upward swings in pressure incident to manipulation of the tumor prior to removal.

Recently Grimson *et al*<sup>42</sup> have reported their experiences in five cases of pheochromocytoma in which an epinephrine competitor regitine<sup>®</sup> has been injected just before operation and several times prior to actual removal of the tumor in an effort to lower sustained hypertension caused by the tumor or to prevent paroxysms incident to manipulation. In the first patient described in an earlier report<sup>41</sup> regitine<sup>®</sup> effectively prevented paroxysms and postoperative collapse. In three of the remaining four although blood pressure was lowered by regitine<sup>®</sup> prior to removal of the tumor immediately thereafter it was necessary to combat hypotension with pitressin or methedrine<sup>®</sup>.

Howard's<sup>60</sup> philosophy is against the use of competitors during operation. He feels that if shock should occur

following removal of the tumor one would be seriously impeded in handling the shock by having the patient full of competitor. Furthermore he believes that most competitors so far developed have central nervous system stimulating effects which may confuse the clinical picture.

Perhaps the two views can be reconciled and permit one to carry a patient through the entire operation with neither upward nor downward swings in pressure by the use of regitine® prior to removal of the tumor and an infusion of dilute epinephrine immediately thereafter. To our knowledge this has not been tried and should first be tried in the animal. Certainly long acting competitors such as dibenamine should not be used nor any competitor which cannot be counteracted with epinephrine.

### **Adrenal Cortical Tumors**

Short of subtotal or total bilateral adrenalectomy rarely if ever indicated in cases of tumor little in the way of special therapy is needed prior to the day of operation. If at exploration it appears probable that in order to effect a cure drastic reduction in the amount of apparently normal adrenal tissue must be accomplished the operation can be terminated and proper premedication instituted several days before the second stage.

We have already discussed hormonal therapy in conjunction with the surgical removal of a cortical tumor causing Cushing's syndrome. Never having observed atrophy of the contralateral adrenal in cases of adrenogenital syndrome secondary to tumor we have not had to use any cortisone in the postoperative management of these cases. Where is adrenal cortical extract and DCA were used in a few instances we question their value. Perhaps with the ready availability of cortisone and because of its low toxicity we should resort to using it routinely in all tumor cases.

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sive survey made in 1950 it was demonstrated conclusively that patients with prostatic cancer who respond favorably to castration and/or estrogen therapy live more comfortably and longer than patients not treated by these methods.<sup>10</sup>

It is equally clear that some patients fail to respond to these forms of treatment and almost all if not all eventually relapse. Much work has been done in an effort to learn why. Much of this has implicated the adrenal.

Largely because of the belief that improvement following castration or estrogen administration was attributable to androgen removal or androgen neutralization it was postulated that in those cases which failed to have a favorable response or in cases that relapsed the adrenals were acting as an extragonadal source of androgen.<sup>11</sup> With this working hypothesis Huggins and Scott<sup>12</sup> in 1945 performed the first total bilateral adrenalectomies in four cases of disseminated prostatic cancer all previously having relapsed after remissions induced by castration estrogen therapy. Managed without cortisone survival times were 1, 3, 11 and 116 days. Obviously no conclusions could be drawn in those surviving only a few days but in the individual who survived 116 days it appeared as if the prostatic cancer progressed although apparently at a retarded rate. Following removal of the second adrenal in the individual surviving the longest urinary 17 keto steroids fell to very low levels and urinary androgens as measured by the comb growth technique were absent. However there was a continued excretion of small amounts of estrogen. These hormonal studies coupled with lack of clinical improvement suggested that some prostatic cancers were "androgen independent."

Because of the great difficulty in overcoming adrenal insufficiency with the steroids then available total bilateral adrenalectomy for widespread prostatic cancer was



## VII

# BILATERAL ADRENALECTOMY IN THE TREATMENT OF DISSEMINATED CANCER OF THE PROSTATE AND BREAST

### INTRODUCTION

IT IS BEYOND the scope of this monograph to review the wealth of evidence which suggests that disseminated cancer of the prostate and breast may be influenced favorably by endocrine measures. Furthermore, at this writing insufficient time has elapsed to permit an accurate evaluation of the measure — *total bilateral adrenalectomy* — which concerns us here. However, because the endocrine approach appears to be the most profitable one at present, a few pages will be devoted to a discussion of this approach to these two cancers.

### DISSEMINATED PROSTATIC CANCER

In 1941 Huggins and his associates published three papers under the general heading *Studies on Prostatic Cancer*<sup>1, 2, 3</sup> which dealt primarily with the effects of castration and estrogen administration in metastatic cancer. This work demonstrated that in the majority of instances these endocrine manipulations resulted in subjective and objective improvement. Confirmation by others followed shortly and continues. Thus in an exten-

miscellaneous malignant tumors which had metastasized

In the series of seven patients with prostatic cancer studied by Huggins and Bergenstal<sup>1</sup> there was one post operative death and they judged that three of the remaining six had a clinical remission of the disease of considerable magnitude. One patient died of acute pulmonary edema 49 days after adrenalectomy. The remaining four had been observed for periods of 4½ to nine months at the time of their report. Quoting them again

### SUBSTITUTION THERAPY FOR TOTAL ADRENALECTOMY

#### 0 Minus 1 Day

Cortisone acetate	50 mg	6 a m	12 noon
Desoxycorticosterone acetate	5 mg	6 p m	12 midnight
Sodium chloride	5 gm		6 a m
			6 p m

#### 0 Day (Day of Operation)

Cortisone acetate	150 mg	7 a m
Desoxycorticosterone acetate	5 mg	7 a m
Operation †		8 a m
Cortisone acetate	50 mg	Every 4 hr

#### 0 Plus 1 Day

Cortisone acetate	50 mg	Every 6 hr
Desoxycorticosterone acetate	5 mg	1 injection
Sodium chloride	3 gm	by mouth

#### 0 Plus 2 Days

Cortisone acetate	50 mg	Every 12 hr
Desoxycorticosterone acetate	0.3 mg	As needed
Sodium chloride	3 gm	

#### Subsequent Days

The dosage of steroids is gradually reduced until the sustaining dose of cortisone acetate (25 to 50 mg daily) is reached about one week after the operation. Desoxycorticosterone acetate is not required for maintenance therapy.

Substitution therapy following bilateral adrenalectomy. (Courtesy of Dr. Charles Huggins and Dr. D. M. Bergenstal.)

Cortisone acetate and desoxycorticosterone acetate were administered throughout by intramuscular injection and the sodium chloride orally.

† Five hundred cubic centimeters of 0.9% sodium chloride and 500 cc of 1% novocaine are injected intravenously during operation and 10 cc of morphine per cubic centimeter is injected when systolic blood pressure falls below 100 mm.

not again performed until early in 1951.<sup>64</sup> In the previous year Harrison Thorn and Criscitello<sup>65</sup> studying the effect of total bilateral adrenalectomy in malignant hypertension and chronic nephritis had demonstrated that with judicious use of fluids salt cortisone and desoxycorticosterone acetate it was possible to overcome adrenal insufficiency and maintain life. At the time of their report (May 1951) nine of 15 patients were alive and seven of these were judged improved both subjectively and objectively. They attributed improvement to the elimination of desoxycorticosterone like factors and regulation of its administration thereafter in such a manner as to avoid excessive retention of sodium and water on the one hand and relative hypotension on the other.

In June 1951 Huggins and Bergenstal<sup>66</sup> reported on two patients with widespread prostatic cancer who survived total adrenalectomy for five and six months and who were in a state of clinical remission at that time. The successful substitution therapy which they devised is reproduced in Figure 36.

Stimulated by this work several different medical groups began studies of the effect of total adrenalectomy not only on prostatic cancer but on other malignant tumors. At the Second National Cancer Conference March 3, 4 and 5 of 1952 we learned of many cases some of which have since been reported. In February 1952 Huggins and Bergenstal<sup>67</sup> reported having performed total adrenalectomy in seven men with disseminated prostatic cancer and in seven women with advanced breast cancer. By June 1952 Huggins<sup>68</sup> had done 38 consecutive total adrenalectomies without an operative fatality. Many of these were for metastatic breast cancer in women (vide *infra*). In September 1952 West *et al*.<sup>69</sup> published the results of their study of 22 total adrenalectomies, 10 in prostatic cancer, six in cancer of the breast and six in

chemicals and estrogens considerable work has been done to determine the relation of estrogens to cancer of the breast. Space does not permit more than a superficial review of this evidence.

In 1916 Lathrop and Loeb<sup>86</sup> demonstrated that the incidence of breast cancer in mice belonging to strains of high incident breast cancer fell to zero in the majority of strains where these mice were oophorectomized at age three to four months. Corn<sup>87</sup> showed that this reduction in incidence varied directly with the age of castration — the earlier the castration the lower the incidence. If castration was done at the age of eight to 10 months the rate became as high as in the control group. However Wooley and co workers<sup>88</sup> showed that when female mice of high cancer strains were castrated immediately after birth the incidence of breast tumors was greater than in mice castrated at maturity. This phenomenon was thought to be due to the production of estrogen by the adrenal cortex.

In 1932 Lacassagne<sup>89</sup> succeeded in producing mammary cancer in males of cancer free strains by the injection of large amounts of estrogenic substances. Subsequently he reported induction of mammary cancer in both high and low incident strains but with much greater difficulty in the latter.<sup>90</sup> Others have confirmed this work and have extended it to show that the carcinogenic effect of estrogens could be counteracted by androgens. Notable among these workers are Raynaud and Lacassagne<sup>91</sup> Murlin and his associates<sup>92</sup> and Nathanson and Aderant<sup>101</sup>

In human breast cancer this principle of utilizing androgens to neutralize the effects of estrogens was voiced simultaneously in 1939 by Loeser<sup>93</sup> and by Ulrich.<sup>122</sup> These authors described favorable changes in patients with advanced breast cancer following the administration

Perhaps the most striking observation has been the immediate and persistent relief of crippling pain in the bones.

The most recent results in the series of 10 patients adrenalectomized for prostatic cancer and reported by West and his associates<sup>144</sup> are in an addendum to their paper. Three died in the immediate postoperative period, one from cerebral hemorrhage (two days), one from carcinomatosis (11 days) and one from myocardial infarction (21 days). Six of the remaining seven died within 33 to 294 days after adrenalectomy, two from adrenal insufficiency and four from cancer. The remaining patient was living at the writing of the addendum, his 159th postoperative day. According to the authors, All seven patients had temporary subjective improvement varying from 14 to 210 days, averaging 82 days. Only two out of the seven had objective improvement lasting 90 to 133 days. Quoting further, The most striking beneficial response to adrenalectomy was relief of pain.

Our own experience is similar (unpublished).

Needless to say the merits of endocrine management will be decided not on any theoretical basis but on its practical value. The belief that these procedures are effective though not curative drives us to study the possible mechanisms involved in the hope that further advances can be made. Those interested in a discussion of possible mechanisms are referred to a rather lengthy account by one of us.<sup>145</sup>

## DISSEMINATED BREAST CANCER

Largely as the result of the association of breast growth and development with ovarian activity and the demonstration of a relationship between certain carcinogenic

chemicals and estrogens considerable work has been done to determine the relation of estrogens to cancer of the breast. Space does not permit more than a superficial review of this evidence.

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### DISSEMINATED BREAST CANCER

Largely as the result of the association of breast growth and development with ovarian activity, and the demonstration of a relationship between certain carcinogenic

presented elsewhere and will not be considered here. Huggins' later report with Dao<sup>67</sup> follows the seven patients originally reported for a longer time and hence is more informative. One more case is added. Of the eight one died 48 hours after operation. Of the remaining seven two had no response to therapy and died at 34 days and six months respectively. Five were living for periods of seven to 11 months and four of these were judged to have had a satisfactory response.

The results of West *et al*<sup>144</sup> are similar. Of the five cases with breast cancer three are now dead. All three died from their neoplastic disease. The postoperative survival in these cases varied from 119 to 170 days, averaging 137 days. Two cases are still alive 169 and 175 days postoperatively. Both of these cases had subjective and objective improvement for approximately 120 days. Both patients showed objective improvement. All five patients showed subjective improvement lasting from 14 to 120 days, averaging 67 days.

The search goes on.



of testosterone propionate. This therapeutic method was applied extensively after the publication of Adair and Herrmann.

In 1944 Binnie<sup>1</sup> in an effort to make advanced breast cancer in the female more radiosensitive noted regression of the tumor in a patient by the use of estrogen alone (diethylstilbestrol). Haddow *et al*<sup>2</sup> subsequently noted favorable changes in 16 of 40 patients treated with estrogen alone. Two years later Nathanson<sup>100</sup> reported definitely favorable to excellent results in 28 of 54 women with advanced cancer of the breast treated with relatively large doses of estrogen.

Since the publications of Adair and Herrmann and Nathanson<sup>100</sup> literally thousands of women with inoperable breast cancers have been treated with either androgens or estrogens. Generally speaking androgens have been more effective in the premenopausal woman and have had a greater effect on skeletal lesions. Improvement following estrogen usually given after the menopause has consisted primarily of changes in the local lesion and in lymph node and pulmonary metastases.

On the basis of experimental data in animals it is difficult to reconcile the apparently paradoxical effects of estrogen in human breast cancer. Theoretically androgen should work better than estrogen. Differences in response may be related to many factors which include the age of the patient, the size of the dose of hormone given, the state of other endocrine glands and the phase of the cancer. Huggins<sup>61</sup> states: "Both methods of treatment are empirical."

Recognizing that other factors may be involved as stated above Huggins and Bergenstil<sup>6</sup> carried out bilateral adrenalectomy in seven women with advanced breast cancer. The theoretical considerations forming the basis for this type of therapy as developed by them are







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*This Book*

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